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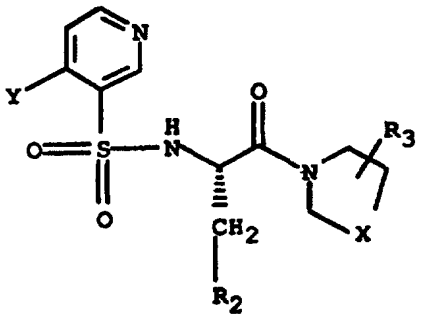

(I)

(57) Abstract

The present invention provides a compound of general formula (I) in which Y is a primary or secondary amino group; R_2 is the residue of a natural or synthetic amino acid; R_3 is hydrogen or a C_1-C_8 alkyl chain which may be substituted by hydroxy or halogen; and X is $(CH_2)_n$ where n is 1, 2, or 3, or is CH_2N or represents a fused phenyl ring which is optionally substituted by one or two methoxy groups or a salt thereof.

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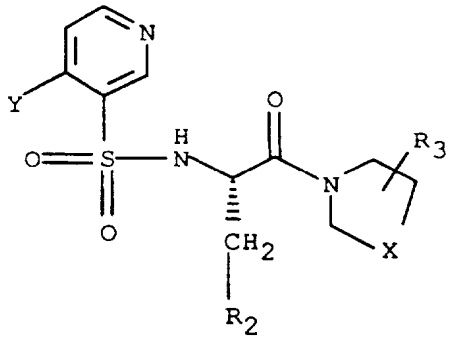
Thrombin Inhibitors

The present invention relates to new compounds which have activity as inhibitors of thrombin.

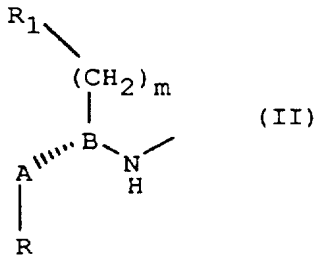
Accordingly the present invention provides a compound of the general formula I



(I)

in which Y is a primary or secondary amino group; R_2 is the residue of a natural or synthetic amino acid; R_3 is hydrogen or a C_1-C_8 alkyl chain which may be substituted by hydroxy or halogen; and X is $(CH_2)_n$ where n is 1, 2, or 3, or is CH_2N or represents a fused phenyl ring which is optionally substituted by one or two methoxy groups or a salt thereof.

As a primary or secondary amino group, Y may have the formula



(II)

in which A and R are absent or A is a methylene or ethylene group, and R is hydrogen, halogen, azido, $COOR_8$ where R_8 is H or alkyl, OR_9 where R_9 is H,

alkyl, optionally substituted hydroxyalkyl, optionally substituted carboxyalkyl, optionally substituted amidoalkyl, SO_2 alkyl, SO_2 aryl, or $NR_{10}R_{11}$ where R_{10} and R_{11} are independently H, alkyl which is optionally substituted and/or optionally interrupted by O or is CH_3SO_2, or together with the nitrogen atom form an optionally substituted ring which may contain another hetero atom or R is SR_{12} where R_{12} is hydrogen or hydroxyalkyl; B is CH or is absent provided that when B is absent, A and R are also absent; R_1 is hydrogen, alkyl, alkyl optionally substituted and/or optionally interrupted by O, S, carboxyl aminocarbonyl, or carbonylamino or is an optionally substituted phenyl ring or a phenyl ring containing one or more heteroatoms or a cyclohexane or bicyclic ring containing one or more hetero atoms; m is 0, 1 or 2 and when m is 1 and R is H, A may form a cyclopropane ring with the C atom to which R_1 is attached.

When R_{10} and R_{11} represent alkyl, the alkyl may be substituted by OH, $COOR_8$ where R_8 is H or alkyl, carbonyl or amide groups or by a heterocyclic ring.

When R_1 is a substituted alkyl group it may be substituted by OH, substituted hydroxyl, carboxyl, carboxyalkyl, phenyl or substituted amino. Preferably the substituent is in a terminal position.

When R_1 is a substituted phenyl ring it may be substituted by one or more halogen or alkyl groups or one or more groups OR_4, SR_5, NR_6R_7 or $COOR_8$ where each of R_4 to R_8 is H or alkyl or NR_6R_7 is NO_2.

Halogen atoms in R and/or R_3 may be fluorine, chlorine, bromine or iodine, but preferably fluorine or chlorine.

Examples of the groups R include H, F, Cl, N_3, OH, OCH_3, OSO_2CH_3, OSO_2 benzyl,
OCH_2CH_2OH and its 2-pyranyl ether, OCH_2COOH and its tert.-butyl ester, $OCH_2CON(CH_3)_2$, $OCH_2CONH(CH_2)_2OH$, the corresponding morpholide $OCH_2COMorph$, COOH and its methyl and tert.-butyl esters, SH, $S(CH_2)_2$ OH, $S(CH_2)_3$ OH, NH_2, $NHCH_3$, NHC_2H_5, $N(CH_3)C_2H_5$, $NHC_3H_7(n)$, NHC_4H_9, $NHCH_2CH_2OH$, $NHCONH_2$, $NHCONHC_2H_5$, $NHCH_2CH_2OCH_3$, $N(CH_2CH_2OCH_3)_2$, $NHCOCH_3$, $N(CH_3)CH_2COOH$, $NHCH_2COOH$ and its tert.-butyl ester, $NHCH_2$ pyridyl, $N(CH_3)_2$, $N(C_2H_5)_2$, pyrrolidinyl, piperidinyl, 4-hydroxypiperidinyl, morpholinyl, thiomorpholinyl.

When R_{10} and R_{11} form a ring together with the nitrogen atom to which they are attached, the ring may be, for example, a piperidine, pyrrolidine, morpholine, thiomorpholine or piperazine ring, which may be optionally substituted.

When R_1 is or contains a ring system, the ring may be, for example, a phenyl, cyclohexane, benzothiazole, indole, indane, naphthalene, thiophene or thiazole ring.

In many cases R_1 is derived from an amino alcohol, for instance, those obtained from optionally ring-substituted phenylalanines, tryptophans and pyridylalanines.

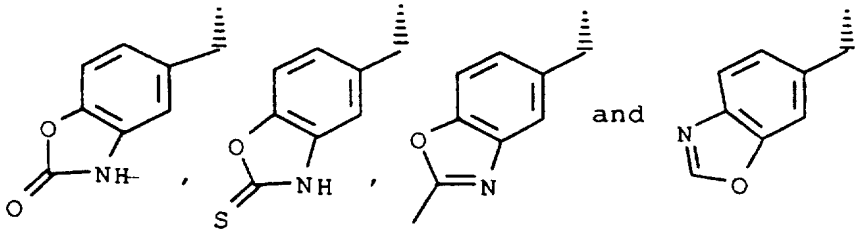
Examples of the group R_1 include phenyl, cyclohexyl, 4-methoxyphenyl, 4-ethoxyphenyl, 3-4-di-methoxyphenyl, 4-fluorophenyl, 3,4-dichlorophenyl, 4-hydroxyphenyl, 4-nitrophenyl, 4-aminophenyl, 4-methylphenyl, 2-pyridyl, thiazolyl, indolyl, methylthiomethyl, n-butyl.

Examples of the group R_1-$(CH_2)_m$ include n-propyl, n-butyl, n-pentyl, iso-butyl, iso-pentyl, 5-hydroxy-pentyl, carboxylethyl, 4-phenylbutyl, n-butylcarbamoylethyl, 2-indanyl, 4-methylbenzyl, 2-aminobenzyl, 4-carboxybenzyl and its methyl ester, 2-pyridylmethyl, phenylethyl, 4-

hydroxyphenylethyl and its methyl ether, 2-aminophenylethyl, carboxyundecyl, hydroxyethyloxyethyl.

As an amino acid residue, R_2 may be derived from the amino acids phenylalanine, tyrosine, dopa and its ethers such as the methylenedioxy ether, p-aminophenylalanine, p-nitrophenylalanine, naphthylalanine, benzothiazolylalanine, thiazolylalanine, cyclohexylalanine, the pyridylalanines, tryptophan, and fused 6/5 membered ring systems linked through the 6-membered ring and where the 5-membered ring contains one or more hetero atoms.

Examples of the groups R_2-CH_2- include 2-benzthiazolylmethyl, 2-benzoxazolylmethyl, 2-benzimidazolylmethyl, 2-naphthylmethyl, 2-(3- and 4-)pyridylmethyl, benzyl, 4-hydroxybenzyl, 4-methoxybenzyl, 4-ethoxybenzyl, cyclohexylmethyl, 4-nitrobenzyl, 4-aminobenzyl, 4-methylaminobenzyl, 4-dimethylaminobenzyl, 4-ethylaminobenzyl, 4-fluorobenzyl, 3,4-dihydroxybenzyl, 3,4-dimethoxybenzyl, 3,4-methylenedioxybenzyl, 4-acetylaminobenzyl, 4-formylaminobenzyl, 4-hydroxyaminobenzyl, 3-hydroxy-4-methoxybenzyl, 3-amino-4-hydroxybenzyl, 3-amino-4-methoxybenzyl, 4-thiazolylmethyl



The group R_3 preferably has 2 or 3 carbon atoms and may be terminally substituted by hydroxy, fluorine or chlorine.

X is preferably CH_2N or $(CH_2)_2$. When X is CH_2N the two N atoms in the ring are preferably in the para positions and R_3 is then preferably attached to the N atom in X.

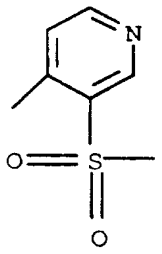
Preferably A-R is present, m is 1, A is $-CH_2-$ and X is $(CH_2)_2$.

There are two chiral centres in the compounds of the invention. It is preferred that the compounds have the (S) configuration at each of the chiral centres. Compounds having the (R) configuration are also included within the scope of the invention especially when it is borne in mind that the priority rules for naming compounds result in an (R) configuration in some cases e.g. where R_1 is a methylthiomethyl group.

The compounds of the invention can be considered as being in four parts, A, an amine moiety which is

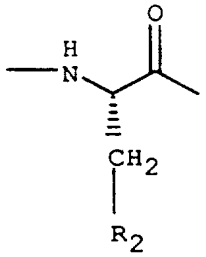
(II)

B, a pyridine moiety which is



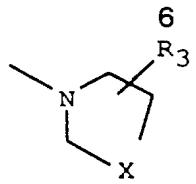
(III)

C, an aminoacid moiety Aa which is



(IV)

and D, a base which is



(V)

The compounds of the invention may be made by various processes as outlined in Methods 1 to 3 below

Synthetic Schemes

Method 1: (D→ C-D→ B-C-D→ A-B-C-D)

Base + N-protected aminoacid
↓ coupling

N-protected aminoacyl base
↓ deprotection

aminoacyl base
↓ chloropyridine sulfonyl chloride

chloropyridinesulfonyl-aminoacyl-base
↓ amine

aminopyridinesulfonyl-aminoacyl-base

Method 2: (B → B-C → B-C-D → A-B-C-D)

chloropyridine sulfonylchloride + aminoacid (derivative)
↓ coupling

chloropyridine sulfonyl-aminoacid (derivative)
↓ deprotection (if needed)

chloropyridine sulfonyl-amino acid
↓ couple with base

chloropyridine sulfonyl-aminoacyl-base
↓ amine

aminopyridine sulfonyl-aminoacyl-base

Method 3: (B→ B-C→ A-B-C→ A-B-C-D)

This is similar to Method 2 except that the last two stages are interchanged.

In all cases it is then possible to convert one amino moiety into a different amino moiety.

In the above Methods 1, 2 and 3, the C-D coupling reaction may be carried out
by reaction of the amino acid with the base and where the amino acid and the base are optionally protected. The reaction of the amino acid with the base is carried out for instance as are coupling reactions of amino acids in the preparation of peptides and according to methods of protection, activation, coupling and deprotection or partial deprotection described in the literature (Houben Weyl, Methoden Der Organichen Chemie Vol. 15 Parts 1 & 2).

For instance the aminoacyl base compounds can be prepared by protecting the α-amino group of the amino acid via acetylation, formylation, phthaloylation, trifluroacetylation, p-methoxybenzyloxycarbonylation, benzoylation, benzyloxycarbonylation, t-butyoxycarbonylation, arylsulfonylation, or tritylation and then condensing the formed N^{α}-substituted amino acid with the base to give a protected form of the aminoacyl base by a conventional process such as the acid chloride method, azide method, mixed anhydride method, activated ester method, or

carbodiimide method, with or without additives such as hydroxysuccinimide, hydroxybenztriazole, diethyl phosphite or the like, and thereafter selectively removing the protective groups to give the desired compound.

Alternatively the reaction may be carried out by the condensation of an N^{α}-arylsulfonyl aminoacyl halide, preferably a chloride, a mixed anhydride, or a similar activated species derived in situ from the amino acid with at least an equimolar amount of the base. The condensation reaction can be carried out with or without an added solvent in the presence of a base. Solvents such as dimethylformamide (DMF) or dimethylacetamide (DMF) or halogenated solvents such as chloroform or dichloromethane may be used. The amount of the solvent to be used is not critical and may vary from about 5 to 100 times the weight of the N^{α}-arylsulfonyl amino acid (VI). In the other cases the activating principle such as diethyl phosphite may be the solvent.

When the activated species is a pyridyl-sulfonyl aminoacyl halide it may be prepared by reacting a pyridyl-sulfonyl amino acid VII with at least an equimolar amount of a halogenating agent such as thionyl chloride, phosphorus oxychloride, phosphorus trichloride, phosphorus pentachloride or phosphorus tribromide. The halogenation may be carried out with or without an added solvent. The preferred solvents are chlorinated hydrocarbons such as chloroform and dichloromethane, and ethers such as tetrahydrofuran and dioxan. Preferred reaction temperatures are in the range of -10°C to room temperature. The reaction time is not critical, but varies with the halogenating agent and reaction temperature. In general, a period of 15 minutes to 5 hours is operable.

Alternatively the reaction may include reaction of the amino acid with the base in the presence of condensing agent such as a carbodiimide, for instance dicyclohexyl-carbodiimide in the presence or absence of an activating species such as hydroxybenzotriazole or diethyl phosphite and in the presence of a base. The base used in the above reactions may be either an organic base such as Huenig Base, triethylamine, N-methylmorpholine, or pyridine or an inorganic base such as sodium

hydroxide or potassium carbonate. The condensation reaction may be carried out at a temperature between -10° C and the boiling point of the solvent. Preferred condensation reaction temperatures are in the range from -10° C to room temperature. The reaction time is not critical. In general, a period of from 5 minutes to 10 hours is operable.

The B-C reaction may be carried out for instance under conditions known for introducing arylsulfonyl groups onto amino substituted compounds.

For instance the reaction may be carried out by the condensation of an aminoacid or aminoacyl amide with a substantially equimolar amount of 4-chloropyridine-3-sulfonyl chloride. The condensation reaction is generally effected in a suitable inert solvent in the presence of an excess of a base, such as an organic base e.g. triethylamine, di-isopropylethylamine, pyridine, N-methyl or N-ethyl morpholine or a solution of an inorganic base e.g. sodium hydroxide or potassium carbonate, at a temperature of 0°C to the boiling temperature of the solvent for a period of 10 minutes to 15 hours. The preferred solvents for the condensation include dichloromethane or other chlorinated hydrocarbons, DMF, benzene-diethyl ether, diethyl ether-water and dioxan-water.

The A-B reaction may be carried out by the condensation of the amine with a chloropyridine sulfonyl compound which already carries the aminoacid moiety and optionally the base as well.

In some cases the amine moiety A may be complex and be derived from 2 or 3 components such as a-b-c or b-c. In these cases the amine can be pre-formed and reacted with the chloropyridine compound B-C-D to form A-B-C-D. Alternatively the amine may be reacted with B-C-D as b-c followed by adding a or it may be reacted as c, then a-b or as c then b then a. In all cases, dependent on the actual structures, it is possible to have protection, or proceed without it. Thus the compounds of the invention may be formed:-

(i) a-b-c + B-C-D → a-b-c-B-C-D

(ii) b-c+B-C-D → b-c-B-C-D, then couple with a → a-b-c-B-C-D

(iii) c+B-C-D → c-B-C-D, then activate as mesylate and displace with a-b → a-b-c-B-C-D

(iv) c+B-C-D → c-B-C-D, then activate as mesylate and displace with b (or a derivative which is then deprotected) → b-c-B-C-D and then couple with a → a-b-c-B-C-D

When the product of formula I is obtained from the condensation reaction in protected form, it may be purified by extraction and the solvent removed by such standard means as evaporation under reduced pressure and then converted to the compound of formula I by removing the protecting group by means of acidolysis or hydrogenolysis. The acidolysis is generally effected by contacting the protected form of I and an excess of an acid such as hydrogen fluoride, hydrogen chloride, hydrogen bromide or trifluoroacetic acid, without a solvent or in a solvent, such as an ether e.g. tetrhydrofuran or dioxan, an alcohol e.g. methanol or ethanol or acetic acid at a temperature of -10°C to 100°C, and preferably at room temperature for a period of 30 minutes to 24 hours. The products are isolated by evaporation of the solvent and the excess acid, or by trituration with a suitable solvent followed by filtration and drying.

Because of the use of excess acid, the products are in certain cases the acid addition salts of the compounds of formula I, which can easily be converted to a free amide by neutralisation. When the protected compound of formula I contains the benzoxycarbonyl protection group the removal is readily accomplished by hydrogenolysis. At the same time any benzyl ester moiety is converted to the carboxyl group by the hydrogenolysis.

The hydrogenolysis is effected in an inert reaction solvent, e.g. methanol, ethanol, tetrahydrofuran or dioxan optionally in the presence of an acid such as acetic acid and in the presence of a hydrogen-activating catalyst e.g. Raney nickel, palladium or platinum, in a hydrogen atmosphere at a temperature of 0°C to the boiling temperature of the solvent for a period of 2 hours to 120 hours. The hydrogen pressure is not critical, and atmospheric pressure is sufficient. The products of formula I are isolated by filtration of the catalyst followed by evaporation of the solvent. They may be purified by trituration or recrystallisation from a suitable solvent, such as ethyl acetate, diethyl ether-tetrahydrofuran, diethyl ether-methanol and water-methanol, or may be chromatographed on silica gel, ion-exclusion gels or reverse-phase liquid chromatography supports.

In those cases where the initial product of formula I contains a protected carboxylic acid or alcohol, it is well recognised in the art that the carboxylic acid or alcohol can be prepared from the ester derivative by conventional hydrolysis or acidolysis methods. The conditions under which esterification, hydrolysis or acidolysis can be carried out will be apparent to those skilled in the art.

The compounds (I) of this invention in certain cases form acid addition salts with any of a variety of inorganic and organic acids. Some of the compounds containing a free carboxyl group form salts with any of a variety of inorganic and organic bases.

The product of the reactions described above can be isolated in the free form or in the form of salts. In addition, the product can be obtained as acid addition salts by reacting one of the free bases with an acid, such as hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, acetic, citric, maleic, succinic, lactic, tartaric, gluconic, benzoic, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic acid or the like. In a similar manner, the product can be obtained as salts by reacting the free carboxylic acid with a base, such as sodium hydroxide, potassium

hydroxide, ammonium hydroxide, triethylamine, procaine, dibenzylamine, N,N'-dibenzylethylenediamine, N-ethylpiperidine or the like.

Likewise, treatment of the salts with a base or acid results in a regeneration of the free amide.

The chloropyridine sulfonyl chloride may be prepared from the corresponding hydroxypyridine sulfonic acid by chlorination.

Examples of suitable chlorinating agents include phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride, phosgene, benzotrichloride, thionyl chloride, chlorosulfonic acid, sulfur dichloride, sulfur and chlorine and chlorine.

Suitable solvents for the reaction include trifluoroacetic acid, dimethylformamide (DMF), dimethylacetamide (DMA), 1,3-dimethyl-2-imidazolidinone (DMID), and pyridine.

The reaction is conveniently carried out between -10°C and the boiling point of the solvent. It is advantageous to disperse or dissolve the sulfonic acid or its salt in the solvent whilst applying ultrasound.

After the reaction is complete, the reaction product is poured into ice water and then extracted with a solvent such as ether, benzene, ethyl acetate, chloroform or the like.

The compounds of the formula I provide interesting compounds which contain potent and orally bioavailable inhibitors of serine proteases, especially thrombin.

The compounds of the present invention are useful in compositions, combinations and methods for the treatment and prophylaxis of various diseases attributed to thrombin-mediated and thrombin-associated functions and processes. These include myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis, disseminated intravascular coagulation, peripheral arterial occlusion, restenosis following arterial injury or invasive cardiological procedures including percutaneous transluminal coronary angioplasty, atrial fibrillation, acute or chronic atherosclerosis, edema and inflammation, various cell regulatory processes (e.g. secretion, shape changes, proliferation), cancer and metastasis, and neurodegenerative diseases.

The thrombin inhibitors of the present invention may be formulated into pharmaceutically useful compositions, such as by mixing with a pharmaceutically acceptable carrier or diluent. These compositions may be used for treating or preventing thrombotic diseases in a patient.

According to an alternate embodiment of the present invention, the thrombin inhibitors may be employed in compositions for preventing and/or treating thrombotic disease, and for decreasing the dosage of a thrombolytic agent required to establish reperfusion or prevent reocclusion in a patient. Additionally, the thrombin inhibitors of this invention may be used in compositions for decreasing reperfusion time or the incidence of acute reocclusion in a patient treated with a thrombolytic agent. These compositions may comprise a pharmaceutically effective amount of a thrombin inhibitor of the present invention and a pharmaceutically effective amount of a thrombolytic agent.

In these compositions, the thrombin inhibitor and the thrombolytic agent work in a complementary fashion to dissolve blood clots, resulting in decreased reperfusion times and incidence of acute reocclusion in patients treated with them. The thrombolytic agent dissolves the clot, while the thrombin inhibitor prevents newly exposed, clot-entrapped or clot-bound

thrombin from regenerating the clot. The use of the thrombin inhibitor in the compositions of this invention advantageously allows the administration of a thrombolytic reagent in dosages previously considered too low to result in thrombolytic effects if given alone. This avoids some of the undesirable side effects associated with the use of thrombolytic agents, such as bleeding complications.

Thrombolytic agents which may be employed in the combinations and compositions of the present invention are those known in the art. Such agents include tissue plasminogen activator purified from natural sources, recombinant tissue plasminogen activator, streptokinase, urokinase, prourokinase, anisolated streptokinase plasminogen activator complex (ASPAC), animal salivary gland plasminogen activators, hybrids of the above and known, biologically active derivatives. The thrombin inhibitor and the thrombolytic agent may be in the same or in separate dosage forms which are administered separately, but concurrently or sequentially. In sequential administration, the thrombin inhibitor may be given to the patient at a time from 5 hours before to 5 hours after administration of the thrombolytic agent. Preferably, the thrombin inhibitor is administered to the patient at a time from 2 hours before to 2 hours after administration of the thrombolytic agent.

The compounds of the invention may also be used in combinations and compositions with other antithrombotic drugs such as aspirin, fibrinogen receptor blockers, platelet glycoprotein IIb/IIIa antagonists, platelet aggregation inhibitors and the like.

The compositions of the invention may be administered to a patient in various ways e.g. enterally such as orally or rectally, parenterally or topically. The compositions will be formulated using adjuvants and diluents suitable for the desired method of administration. Thus the compositions may be administered intravenously or intra-arterially as bolus or by continued infusion, intramuscularly - including paravertebrally and periarticularly - subcutaneously, intracutaneously, intra-articularly, intrasynovially,

intrathecally, intra-lesionally, periostally or by oral, nasal or topical routes. In addition they may be given by either passive or active methods, including by iontophoresis.

Parenteral compositions are preferably administered intravenously either in a bolus form or as an infusion. For parenteral administration, the thrombin inhibitor may be either suspended or dissolved in a sterile vial or ampoule and sealing. Preferably, adjuvants such as a local anesthetic, preservatives, stabilizers, solution promoters and/or buffers may also be dissolved in the vehicle. The composition may then be
frozen and lyophilized to enhance stability. In the case of suspensions, a surfactant or wetting agent and/or other adjuvant as mentioned above may be included in the composition to facilitate uniform distribution of its components.

Tablets and capsules e.g. gelatin capsules for oral administration may comprise the active ingredient together with a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salts and/or polyethylene glycol; for tablets also c) binders, e.g. magnesium aluminium silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellolose and/or polyvinylpyrrolidone; if desired, d) disintegrants, e.g. starches, starch derivatives such as sodium starch glycolate, croscarmellose, agar, alginic acid or its sodium salt, or effervescent mixtures; e) wetting agents such as sodium lauryl sulphate; and/or f) absorbents, colourants, flavours and sweeteners. Suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents.

Oral liquid preparations may be in the form of aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstruction with water or another suitable vehicle before use. Such liquid preparations may contain conventional additives. These include

suspending agents; such as sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, such as lecithin, sorbitan monooleate, polyethylene glycols, or acacia; non-aqueous vehicles, such as almond oil, fractionated coconut oil, and oily esters; and preservatives, such as methyl or propyl p-hydroxybenzoate or sorbic acid.

Compositions formulated for topical administration may, for example, be in aqueous jelly, oily suspension or emulsified ointment form.

Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1 to 75%, preferably about 1 to 50%, of the active ingredient.

Transdermal systems may be made by applying an adhesive layer to a base layer, e.g. a peel-off protective layer, applying a reservoir to the base layer, the
reservoir containg the active ingredient and optionally a polymeric material for forming a porous or permeable membrane and/or a penetration enhancer, and then applying an impermeable outer layer on top.

The dosage of active compound administered is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, and on the form of administration.

A preferred pharmaceutically effective dose of the thrombin inhibitor of this invention is from 0.01 mg/kg body weight of the patient to be treated to 50 mg/kg body weight, preferably from 0.1 to 1.0 mg/kg.

The amount used depends on the method of administration. Normally lower amounts are needed for parental administration than for enteral administration. The dose for infusions however may be higher than the range given, preferably from 0.01 to 1.0 mg/kg/hr. When a thrombolytic agent is also used a pharmaceutically effective dose of the thrombolytic

agent may be between 10% and 80% of the conventional dosage range, i.e. the dosage used when that agent is employed in a monotherapy.

The compounds of the invention may also be used in the form of conjugates with materials such as polyethylene glycol. This would modify the pharmacokinetic properties of the compounds and result in lower doses being needed, or less frequent doses.

The thrombin inhibitors of the invention may also be used in compositions and methods for coating the surfaces of invasive or extra-corporeal devices, resulting in a lower risk of clot formation or platelet activation in patients receiving or using such devices. Surfaces that may be coated with the compositions of this invention include, for example, prostheses, artificial valves, vascular grafts, stent tubing, membranes and catheters. Methods for coating these devices are known to those of skill in the art. These include chemical cross-linking or physical adsorption of the thrombin inhibitor-containing compositions on to the surfaces of the devices.

Compositions containing the thrombin inhibitors of this invention may also be used in the treatment of tumor metastases, as indicated by the inhibition of metastatic growth. Examples of metastatic tumors which may be treated by the thrombin inhibitors of this invention include carcinoma of the brain, carcinoma of the liver, carcinoma of the lung, osteocarcinoma and neoplastic plasma cell carcinoma.

Compositions containing the thrombin inhibitors of the invention may also be used to inhibit thrombin-induced endoethelial cell activation, including the repression of synthesis of mediators, including platelet-activating factor (PAF), eicosanoids, endothelial-derived relaxing factor (EDRF) and endothelin, by endothelial cells. The compositions have important applications in the treatment of diseases characterised by thrombin-induced inflammation and edema, which is thought to be mediated by PAF. Such diseases include adult respiratory distress syndrome, septic shock,

septicemia, reperfusion damage, and for treating or preventing septicemia and other diseases.

The thrombin inhibitors of the invention or compositions comprising them, may also be used as anticoagulants for extracorporeal blood, for instance in such processes as dialysis procedures, blood filtration, or blood bypass during surgery at doses from 0.01 to 1.0mg/kg as well as in blood products which are stored extracorporeally for eventual administration to a patient and blood collected from a patient to be used for various assays. Such products include whole blood, plasma, or any blood fraction in which inhibition of coagulation is desired.

The amount or concentration of thrombin inhibitor in these types of compositions is based on the volume of blood to be treated or, more preferably, its thrombin content, and may be from 0.01mg/60ml of extracorporeal blood to 5mg/60ml of extracorporeal blood.

The thrombin inhibitors of this invention may also be used to inhibit clot-bound thrombin, which is believed to contribute to thrombus growth and clot accretion, and to prevent thrombus extension. This is particularly important because commonly used anti-thrombin agents, such as heparin and low molecular weight heparin, are ineffective against clot-bound thrombin.

Finally, the inhibitors of this invention may be used for treating neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, inflammatory diseases and cerebral ischaemia.

The invention is illustrated by the following Examples, in which the abbreviations used have the following meanings.

ABBREVIATIONS

DAST	Diethylamino sulfur trifluoride
DME	Ethylene glycol dimethyl ether
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
Huenig Base	Ethyldiisopropylamine
Ishikawa reagent	Diethyl-(1,1,2,3,3,3-hexafluoro-propyl)-amine
NMM	N-Methyl morpholine
PyBOP	Benzotriazol-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate
TBAF	Tetrabutylammonium fluoride
THF	Tetrahydrofuran

Intermediate 1 - 2(S)-Amino-3-(4-fluoro-phenyl)-propan-1-ol

2(S)-Amino-3-(4-fluoro-phenyl)-propionic acid (504mg) is suspended with stirring in dry THF (10ml) and borane/THF complex (1M, 5.5ml) is added over a period of 5 minutes. The mixture is stirred at 20°C for 18 hours and a solution of acetic acid in methanol, (1:4, by vol., 20ml) is added. Solvents are removed by rotary evaporation to give a yellow oil which is purified by spinning band chromatography on silicagel (layer thickness 2mm) using portions (100ml) of chloroform:ethanol (9:1 then 7:3, by vol.) as eluant to give pure 2(S)-amino-3-(4-fluoro-phenyl)-propan-1-ol as a white solid. It has a 1H NMR spectrum consistent with the claimed structure.

Intermediate 2 - 2-[4-(2(S)-Amino-3-phenyl-propyl)-piperazin-1-yl]-ethanol

a) Methanesulfonic acid 2(S)-benzyloxycarbonylamino-3-phenyl-propyl ester (1g) and 2-piperazin-1-yl-ethanol (1.78g) are dissolved in ethanol (80ml) and the solution is heated at reflux for 48 hours. The solvent is removed by rotary evaporation and the resulting oil purified by chromatography on a column of silicagel using chloroform:methanol (19:1 then 37:3, by vol.) as eluant to give 2-[4-(2(S)-benzyloxycarbonylamino-3-phenyl-propyl)-piperazin-1-yl]-ethanol.

b) 2-[4-(2(S)-Benzyloxycarbonylamino-3-phenyl-propyl)-piperazin-1-yl]-ethanol (3.4g) is dissolved in methanol (300ml) and hydrogenated (1 bar) in the presence of palladium on charcoal (10% w/w, 500mg) for 27 hours at 20°C. The catalyst is removed by filtration and the filtrate dried by rotary evaporation to give 2-[4-(2(S)-amino-3-phenyl-propyl)-piperazin-1-yl]-ethanol as a light yellow solid.

Intermediate 3 - 2-{2-[4-(2(S)-Amino-3-phenyl-propyl)-piperazin-1-yl]-ethoxy}-ethanol

Analogously as described for the synthesis of Intermediate 2 but using 1-(2-hydroxyethyloxy-ethyl)-piperazine in place of 2-piperazin-1-yl-ethanol is prepared the title compound as a white solid. It has a 1H NMR spectrum consistent with the claimed structure.

Intermediate 4 - 2(S)-Amino-3-(4-ethoxy-phenyl)-propan-1-ol

2(S)-tert.-Butoxycarbonylamino-3-(4-ethoxy-phenyl)-propionic acid (4.8g) is dissolved in dry THF (25ml) and borane:THF complex (1M, 98ml) is added with stirring under an atmosphere of nitrogen at 0°C over a period of 30 minutes. The mixture is stirred at 20°C for 64 hours, aqueous acetic acid

(10% by vol., 30ml) is added and solvents are removed by rotary evaporation to give a white slurry which is re-evaporated to dryness from solution in portions (x2) of ethanol (20ml) to yield a colourless syrup. This is purified by chromatography on a column of silicagel using mixtures of chloroform:methanol (from 19:1 to 10:10 in 5% increments, by vol.) to give 2(S)-amino-3-(4-ethoxy-phenyl)-propan-1-ol which contains some of the corresponding acid as impurity (confirmed by 1H and 13C NMR spectra).

Intermediate 5 - N-(2(S)-Amino-3-phenyl-propyl)-methanesulfonamide

a) 1(S)-Aminomethyl-2-phenyl-ethyl carbamic acid benzyl ester (4.7g) and triethylamine (5.8ml) are dissolved in dichloromethane (100ml) and placed under an atmosphere of nitrogen. The solution is cooled to 0°C and methane sulfonyl chloride (1.54ml) is added. The mixture is stirred at 0°C for 30 minutes, further portions of methane sulfonyl chloride (0.26ml) and triethylamine (1.2ml) are added and the mixture is stirred for 16 hours at 20°C. Dichloromethane (100ml) is added and the solution is washed with aqueous hydrochloric acid (200ml), brine (200ml), dried ($MgSO_4$) and solvent removed by rotary evaporation to afford pure [1(S)-(methanesulfonylamino-methyl)-2-phenyl-ethyl]-carbamic acid benzyl ester as a white solid. It has 1H and 13C NMR spectra consistent with the claimed structure.

b) [1(S)-(Methanesulfonylamino-methyl)-2-phenyl-ethyl]-carbamic acid benzyl ester (5.6g) is dissolved in a mixture of aqueous hydrochloric acid (10ml), ethanol (300ml) and
dichloromethane (2ml) and hydrogenated (1 bar) in the presence of 10% palladium on charcoal (10%w/w, 600mg) for 2 days at 20°C. Catalyst is removed by filtration and the solvents removed by rotary evaporation. The residue is partitioned between aqueous sodium hydroxide solution (1M, 200ml) and dichloromethane (200ml) and the organic phase is washed with brine (400ml), dried ($MgSO_4$) and solvent removed by rotary evaporation to

afford pure N-(2(S)-amino-3-phenyl-propyl)-methanesulfonamide as a white solid. It has 1H and 13C NMR spectra consistent with the claimed structure.

Intermediate 6 - Piperidine-4-carboxylic acid propylamide

a) Piperidine-1,4-dicarboxylic acid mono-tert.-butyl ester (11.04g) is dissolved in dichloromethane (200ml) and 1,1-carbonyl di-imidazole (17.9g) followed by propylamine (9.4ml) are added to the stirred solution under an atmosphere of nitrogen. The mixture is stirred at 20°C for 16 hours, washed with aqueous citric acid solution (3 x 200ml), saturated aqueous sodium hydrogen carbonate solution (200ml) and brine (200ml), dried ($MgSO_4$) and solvent removed by rotary evaporation to afford pure 4-propylcarbamoyl-piperidine-1-carboxylic acid tert.-butyl ester as a white solid. It has 1H and 13C NMR spectra consistent with the claimed structure. $[M+H]^+ = 271.2$.

b) 4-Propylcarbamoyl-piperidine-1-carboxylic acid tert.-butyl ester (12.34g) is dissolved in dichloromethane (100ml) and trifluoroacetic acid (17.6ml) is added dropwise to the stirred solution over a period of 5 minutes. The mixture is stirred at 20°C for 16 hours, solvents removed by rotary evaporation and the residue partitioned between aqueous sodium hydroxide solution (4M, 180ml) and dichloromethane (200ml). The separated aqueous phase is extracted with further portions (x3) of dichloromethane (200ml) and the combined extracts are dried ($MgSO_4$) and solvent removed by rotary evaporation to afford pure piperidine-4-carboxylic acid propylamide as a white solid. It has 1H and 13C NMR spectra consistent with the claimed structure. $[M+H]^+ = 171.1$.

Intermediate 7 - 2-Phenyl-1(S)-pyrrolidin-1-ylmethyl-ethylamine

a) Methanesulfonic acid 2(S)-benzyloxycarbonylamino-3-phenyl-propyl ester (10g) is dissolved in dichloromethane (200ml) and pyrrolidine (23ml) is

added. The mixture is stirred for 16 hours at 20°C. Solvent is removed by rotary evaporation and the residue is dissolved in ethanol (200ml) and stirred for 16 hours at 50°C. Solvent is removed by rotary evaporation and the residue is dissolved in dichloromethane (100ml). The solution is washed with portions (2x50ml) of water and brine, dried ($MgSO_4$) and solvent removed by rotary evaporation. The residue is purified by flash chromatography on a column of silicagel using dichloromethane:ethyl acetate (4:1, by vol.) as eluant to give (2-phenyl-1(S)-pyrrolidin-1-ylmethyl-ethyl)-carbamic acid benzyl ester.

b) (2-Phenyl-1(S)-pyrrolidin-1-ylmethyl-ethyl)-carbamic acid benzyl ester is dissolved in methanol and catalytically reduced using standard conditions to give 2-phenyl-1(S)-pyrrolidin-1-ylmethyl-ethylamine as an oil.

Intermediate 8 - 1(S)-Morpholin-4-ylmethyl-2-phenyl-ethylamine

a) Methanesulfonic acid 2(S)-benzyloxycarbonylamino-3-phenyl-propyl ester (10g) is dissolved in dry DMF (100ml) and morpholine (24ml) is added. The mixture is heated at reflux for 30 minutes, the solvent removed by rotary evaporation and the residue purified by flash chromatography on a column of silicagel which is eluted with hexane:ethyl acetate (1:1, by vol.) to give (1(S)-morpholin-4-ylmethyl-2-phenyl-ethyl)-carbamic acid benzyl ester as a colourless oil. It has a 1H NMR spectrum consistent with the claimed structure.

b) (1(S)-Morpholin-4-ylmethyl-2-phenyl-ethyl)-carbamic acid benzyl ester (6g) is dissolved in ethanol (150ml) and hydrogenated (1 bar) in the presence of palladium on charcoal (10% w/w, 600mg) for 3 hours at 20°C. Catalyst is removed by filtration and the solvent by rotary evaporation to give 1(S)-morpholin-4-ylmethyl-2-phenyl-ethylamine as a white, waxy solid. It has a 1H NMR spectrum consistent with the claimed structure.

Intermediate 9 -1-(2(S)-Amino-3-phenyl-propyl)-piperidin-4-ol

Analogously as described for Intermediate 8 but starting from 4-hydroxy-piperidine in place of morpholine is prepared 1-(2(S)-amino-3-phenyl-propyl)-piperidin-4-ol as a colourless oil. It has a 1H NMR spectrum consistent with the claimed structure.

Intermediate 10 - 3(S)-Amino-4-phenyl-butan-1-ol

a) 3-Amino-4-phenyl-butyric acid tert.-butyl ester (1.2g) is dissolved in dry dichloromethane (30ml) and converted by standard procedures to the derivative 3(S)-benzyloxycarbonylamino-4-phenyl-butyric acid tert.-butyl ester. It is purified by flash chromatography on a column of silicagel which is eluted with hexane:ethyl acetate (3:1, by vol.) to give the product as a colourless oil. It has a 1H NMR spectrum consistent with the claimed structure.

b) 3(S)-Benzyloxycarbonylamino-4-phenyl-butyric acid tert.-butyl ester is saponified using standard conditions to give 3(S)-benzyloxycarbonylamino-4-phenyl-butyric acid as a white solid. It has a 1H NMR spectrum consistent with the claimed structure.

c) 3(S)-Benzyloxycarbonylamino-4-phenyl-butyric acid (1.7g) is dissolved in dry DME (10ml) and the solution is cooled to -15°C. 4-Methylmorpholine (0.53ml) is added followed by isobutyl chloroformate (0.65ml). The precipitate is removed by filtration and washed with a little DME. A solution of sodium borohydride (0.36g) in water (5ml) is added to the combined cold filtrate and washings followed by water (100ml). The resulting suspension is extracted with portions (3x) of ethyl acetate (25ml) and the combined extracts are dried ($MgSO_4$) and the residue purified by flash chromatography on a

column of silicagel which is eluted with hexane:ethyl acetate (1:1, by vol.) to give (1(S)-benzyl-3-hydroxy-propyl)-carbamic acid benzyl ester as a white solid. It has a 1H NMR spectrum consistent with the claimed structure.

c) (1(S)-Benzyl-3-hydroxy-propyl)-carbamic acid benzyl ester (1.2g) is dissolved in ethanol (50ml) and hydrogenated (1 bar) in the presence of palladium on charcoal (10% w/w, 150mg) for 2 hours at 20°C. Catalyst is removed by filtration and solvent by rotary evaporation to give 3(S)-amino-4-phenyl-butan-1-ol as a colourless oil. It has a 1H NMR spectrum consistent with the claimed structure.

Intermediate 11 - (2(S)-Benzyloxycarbonylamino-3-phenyl-propoxy)-acetic acid

a) (1(S)-Hydroxymethyl-2-phenyl-ethyl)-carbamic acid benzyl ester (10g) is dissolved in dichloromethane (60ml) and bromo-acetic acid tert.-butyl ester (5.7ml) is added with vigorous stirring followed by the addition of aqueous sodium hydroxide (50% w/v, 20ml) and tetrabutylammonium hydrogen sulfate (13g). The mixture is stirred at 20°C for 30 minutes and the suspension washed with water (150ml). The organic phase is dried by rotary evaporation and the residue stirred for 30 minutes in ether (25ml). The suspension is washed with water (15ml), the organic phase is dried ($MgSO_4$) and the residue purified by flash chromatography on a column of silicagel which is eluted with hexane:ethyl acetate (4:1, by vol.) to give (2(S)-benzyloxycarbonylamino-3-phenyl-propoxy)-acetic acid tert.-butyl ester as a colourless oil. It has a 1H NMR spectrum consistent with the claimed structure.

b) (2(S)-Benzyloxycarbonylamino-3-phenyl-propoxy)-acetic acid tert.-butyl ester (1.9g) is dissolved in methanol (100ml) and saponified with aqueous sodium hydroxide under standard conditions. After work-up, (2(S)-benzyloxycarbonylamino-3-phenyl-propoxy)-acetic acid is obtained as a white solid on precipitation from alkaline solution by neutralisation (aqeous hydrochloric acid). It has a 1H NMR spectrum consistent with the claimed structure.

Intermediate 12 - (2(S)-Amino-3-phenyl-propoxy)-acetic acid tert.-butyl ester

(2(S)-Benzyloxycarbonylamino-3-phenyl-propoxy)-acetic acid tert.-butyl ester is catalytically reduced using standard conditions as described for Intermediate 10(c) to give the title compound as a colourless oil. It has a 1H NMR spectrum consistent with the claimed structure.

Intermediate 13 - 1-(2(S)-Benzyloxycarbonylamino-3-phenyl-propyl)-piperidine-4-carboxylic acid

a) Methanesulfonic acid 2(S)-benzyloxycarbonylamino-3-phenyl-propyl ester (22.7g) and piperidine 4-carboxylic acid ethyl ester (58.3g) are dissolved in ethanol (150ml) and heated at 70°C for 7 hours. Solvent is removed by rotary evaporation and the residue is purified by flash chromatography on a column of silicagel using dichloromethane:methanol (49:1, by vol.) as eluant to give 1-(2(S)-benzyloxycarbonylamino-3-phenyl-propyl)-piperidine-4-carboxylic acid ethyl ester as a colourless oil. It has 1H and 13C spectra consistent with the claimed structure.

b) 1-(2(S)-Benzyloxycarbonylamino-3-phenyl-propyl)-piperidine-4-carboxylic acid ethyl ester (17g) is dissolved in ethanol (200ml) and aqueous sodium hydroxide (1M, 200ml) is added. The mixture is stirred at 20°C for 1 hour and

aqueous hydrochloric acid (37% w/v, 16.67ml) is added slowly with stirring under ice cooling. Solvents are removed by rotary evaporation and the solid residue is extracted with portions (4 x 150ml) of methanol. The combined extracts are evaporated and the solid suspended in a mixture of acetone (150ml) and methanol (100ml). After filtration, the filtrate is evaporated to give 1-(2(S)-benzyloxycarbonylamino-3-phenyl-propyl)-piperidine-4-carboxylic acid.

Intermediate 14 - [1-(2(S)-Amino-3-phenyl-propyl)-piperidin-4-yl]-morpholin-4-yl-methanone

a) 1-(2(S)-Benzyloxycarbonylamino-3-phenyl-propyl)-piperidine-4-carboxylic acid (1g) is dissolved in dichloromethane (25ml) and 1,1-carbonyl di-imidazole (613mg) is added under an atmosphere of nitrogen. The mixture is stirred at 20°C for 1 hour and morpholine (264mg) is added. The mixture is stirred for 4 hours, solvents are removed by rotary evaporation and the residue is purified by flash chromatography on a column of silicagel using dichloromethane:methanol (99:1 then 49:1, by vol.) as eluant to give [1-(2(S)-benzyloxycarbonylamino-3-phenyl-propyl)-piperidin-4-yl]-morpholin-4-yl-methanone. It has 1H and 13C spectra consistent with the claimed structure. $[M+H]^+$ = 466.3.

b) [1-(2(S)- Benzyloxycarbonylamino-3-phenyl-propyl)-piperidin-4-yl]-morpholin-4-yl-methanone (660mg) is dissolved in methanol (100ml) and hydrogenated (1 bar) in the presence of 10% (w/w) palladium on charcoal (100mg) for 3 hours at 20°C. Catalyst is removed by filtration and the filtrate is evaporated to give [1-(2(S)-amino-3-phenyl-propyl)-piperidin-4-yl]-morpholin-4-yl-methanone. It has a 1H spectrum consistent with the claimed structure.

Intermediate 15 - 2-Phenyl-1(S)-[2-(tetrahydro-pyran-2(RS)-yloxy)-ethoxymethyl]-ethylamine

a) 2(S)-Dibenzylamino-3-phenyl-propan-1-ol (2.5g) is dissolved in a suspension of sodium hydride (678mg) in dry DMF (27ml) at 0°C under an atmosphere of nitrogen and 2(RS)-(2-bromo-ethoxy)-tetrahydro-pyran (2.11g) is added slowly. The mixture is heated at reflux for 21 hours, cooled and excess of reagent quenched by the slow addition of water. Solvents are removed by rotary evaporation and the residue is purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (3:17, by vol.) as eluant to give dibenzyl-{2-phenyl-1(S)-[2-(tetrahydro-pyran-2(RS)-yloxy)-ethoxymethyl]-

ethyl}-amine as a colourless oil. It has 1H and 13C NMR spectra consistent with the claimed structure. $[M+H]^+ = 460.1$.

b) Dibenzyl-{2-phenyl-1(S)-[2-(tetrahydro-pyran-2(RS)-yloxy)-ethoxymethyl]-ethyl}-amine (490mg) is dissolved in methanol (15ml) and hydrogenated (1 bar) in the presence of 10% (w/w) palladium on charcoal (100mg) for 21 hours at 20°C. Catalyst is removed by filtration and solvent evaporated to give pure 2-phenyl-1(S)-[2-(tetrahydro-pyran-2(RS)-yloxy)-ethoxymethyl]-ethylamine as a colourless oil. It has has 1H and 13C NMR spectra consistent with the claimed structure. $[M+H]^+ = 279.8$.

Intermediate 16 - 2-[4-(2(S)-Amino-3-phenyl-propyl)-piperazin-1-yl]-1-morpholin-4-yl-ethanone

a) Methanesulfonic acid 2(S)-benzyloxycarbonylamino-3-phenyl-propyl ester (4.53g) is dissolved in ethanol (50ml) and 1-(2-morpholin-4-yl-2-oxo-ethyl)-piperazine (7.98g) is added. The mixture is stirred at 50°C for 4 hours, further amine (4g) is added and the mixture is stirred at 70°C for 18 hours

and then heated at reflux for 2 hours. Solvent is removed from the cooled mixture by rotary evaporation and the residue is purified by flash chromatography on a column of silicagel using ethanol:ethyl acetate (3:1, by vol.) as eluant to give {1(S)-[4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazin-1-ylmethyl]-2-phenyl-ethyl}-carbamic acid benzyl ester as a pale yellow foam. It has 1H and 13C NMR spectra consistent with the claimed structure. $[M+H]^+$ = 481.3.

b) {1(S)-[4-(2-Morpholin-4-yl-2-oxo-ethyl)-piperazin-1-ylmethyl]-2-phenyl-ethyl}-carbamic acid benzyl ester (3.92g) is dissolved in ethanol (50ml) and hydrogenated (1 bar) in the presence of 10% (w/w) palladium on charcoal (500mg) for 18 hours at 20°C. Catalyst is removed by filtration and solvent evaporated to give pure 2-[4-(2(S)-amino-3-phenyl-propyl)-piperazine-1-yl]-1-morpholin-4-yl-ethanone as a clear oil. It has 1H and 13C NMR spectra consistent with the claimed structure. $[M+H]^+$ = 347.1.

Intermediate 17 - 1-(2(S)-Amino-3-phenyl-propyl)-piperidine-4-carboxylic acid ethyl ester

a) Methanesulfonic acid 2(S)-benzyloxycarbonylamino-3-phenyl-propyl ester (22.7g) is dissolved in ethanol (100ml) and piperidine-4-carboxylic acid ethyl ester (58.9g) is added. The mixture is stirred at 70°C for 6 hours, cooled and solvent removed by rotary evaporation. The residue is purified by flash chromatography on a column of silicagel using ethyl acetate: hexane (1:1, by vol.) as eluant to give 1-(2(S)-benzyloxycarbonylamino-3-phenyl-propyl)-piperidine-4-carboxylic acid ethyl ester as a yellow oil. It has 1H and 13C NMR spectra consistent with the claimed structure. $[M+H]^+$ = 425.1.

b) 1-(2(S)-Benzyloxycarbonylamino-3-phenyl-propyl)-piperidine-4-carboxylic acid ethyl ester (22.36g) is dissolved in ethanol (100ml) and hydrogenated (1 bar) in the presence of 10% (w/w) palladium on charcoal (3g) for 20 hours at

20°C. Catalyst is removed by filtration and solvent evaporated to give pure 1-(2(S)-amino-3-phenyl-propyl)-piperidine-4-carboxylic acid ethyl ester as a yellow oil. It has 1H and 13C NMR spectra consistent with the claimed structure. $[M+H]^+ = 291.2$.

Intermediate 18 - 2-[2(S)-Amino-3-(4-methoxy-phenyl)-propoxy]-ethanol

a) [1(S)-Hydroxymethyl-2-(4-methoxy-phenyl)-ethyl]-carbamic acid tert.-butyl ester (0.85g) and bromo-acetic acid tert.-butyl ester (1.88ml) are dissolved in dichloromethane (10ml) and aqueous sodium hydroxide solution (50% w/v, 20ml) and tetrabutylammonium hydrogen sulfate (1.02ml) are added under vigorous stirring. The mixture is stirred at 20°C for 1 hour. Water (50ml) and ethyl acetate (50ml) are added and the organic phase is separated. The aqueous phase is extracted with ethyl acetate (25ml) and the combined organic phases are washed with portions (50ml) of saturated aqueous sodium bicarbonate and brine, dried ($MgSO_4$) and the solvent removed by rotary evaporation to give [2(S)-tert.-butoxycarbonylamino-3-(4-methoxy-phenyl)-propoxy]-acetic acid tert.-butyl ester which

contains some bromo-acetic acid tert.-butyl ester. This is confirmed by the 1H NMR spectrum which is consistent with the claimed structure. $[M+H]^+ = 396.2$

b) [2(S)-tert.-Butoxycarbonylamino-3-(4-methoxy-phenyl)-propoxy]-acetic acid tert.-butyl ester (1.94g) is dissolved in dry THF (20ml) and lithium aluminium hydride (1M in THF, 37.9ml) is added with stirring to the solution at 0°C under an atmosphere of nitrogen. The stirred solution is allowed to warm to room temperature and is stirred for a further hour. Crushed ice is added slowly to destroy excess of reagent, water (100ml) and ethyl acetate (50ml) are added and the organic phase is separated. The aqueous phase is washed with portions (2 x 75ml) of ethyl acetate and the combined organic

phases are washed with brine (75ml), dried ($MgSO_4$) and the solvent removed by rotary evaporation to give the crude product as an oil. This is purified by flash chromatography on a column of silicagel using dichloromethane:methanol (4:1, by vol.) as eluant to give pure 2-[2(S)-amino-3-(4-methoxy-phenyl)-propoxy]-ethanol. It has a 1H spectrum consistent with the claimed structure. $[M+CH_5]^+ = 240.0$.

The following Examples are synthesised using the Intermediates described and other known compounds.

EXAMPLE 1

a) Method 1

i) 4-(2-Hydroxy-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester (5.15g) is dissolved in fluorotrichloromethane (15ml) and cooled to -78°C in an atmosphere of dry nitrogen. A solution of DAST (3.55ml) in fluorotrichloromethane (15ml) is added and the mixture is stirred with exclusion of moisture for 10 minutes at -78°C and then allowed to warm to room temperature. After a further 30 minutes, the mixture is poured into ice-water (30ml) and the organic phase separated, washed with brine (2x10ml), dried ($MgSO_4$) and the solvent removed by evaporation at reduced pressure to give a residue which is purified by flash chromatography on a column of silicagel using ether:hexane (1:1, by vol.) as eluant. Appropriate fractions are combined and the solvent removed to give 4-(2-fluoro-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester.

ii) 4-(2-Fluoro-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester (2.2g) is dissolved in saturated hydrogen chloride in acetic acid (12ml) and the solution stirred for 2 hours at 20°C. The solvent is removed by evaporation at reduced pressure and portions of methanol (2x50ml) are evaporated from

the residue to give 4-(2-fluoro-ethyl)-piperidine hydrochloride which is held in vacuo (NaOH pellets).

Method 2

4-(2-Hydroxy-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester (6.53g) is dissolved in dichloromethane (29ml) and the solution is heated to 80°C at 2 bar (autoclave). Ishikawa reagent (7.29g) dissolved in dichloromethane (8ml) is added over a period of 1 hour under pressure and the mixture is heated for 1.5 hours at 12 bar at 80°C. The cooled mixture is washed with portions (2x20ml) of 50% brine and 50% brine buffered to pH4-5. The organic phase is dried (Na_2SO_4) and solvent removed by rotary evaporation to give an oil which is purified by flash chromatography on a column of silicagel using hexane:ethyl acetate (10:1, by vol.) as eluant to give pure 4-(2-fluoro-ethyl)-piperidine-1-carboxylic acid tert.-butyl ester as a light yellow oil. This is converted to 4-(2-fluoro-ethyl)-piperidine hydrochloride as described in Method 1 above.

Method 3

i) [4-(2-Hydroxy-ethyl)-piperidin-1-yl]-phenyl-methanone (31.5g) is dissolved in dichloromethane (200ml) and pyridine (10.9ml) and methanesulfonyl chloride (11.5ml) are added. The mixture is stirred for 2 hours and the volume reduced to 50ml by evaporation, ethyl acetate (250ml) is added and the solution is washed with portions (250ml) of saturated aqueous sodium bicarbonate and water, the organic phase is dried ($MgSO_4$) and evaporated to give methanesulfonic acid 2-(1-benzoyl-piperidin-4-yl)-ethyl ester as a waxy solid which is sufficiently pure for use without further purification.

ii) Methanesulfonic acid 2-(1-benzoyl-piperidin-4-yl)-ethyl ester (41.5g) is dissolved in acetonitrile (150ml), powdered molecular sieve (4 Angstrom) is added followed by TBAF (1M in THF, 145ml) and the mixture is heated at reflux with exclusion of moisture for 2 hours. The mixture is cooled, filtered

and the filtrate washed with saturated aqueous sodium bicarbonate (2x200ml) and brine (200ml), dried ($MgSO_4$) and the solvent evaporated to give an orange oil. Purification by flash chromatography on a column of silicagel using hexane:ether (1:1, by vol.) and then ether as eluants gives [4-(2-fluoro-ethyl)-piperidin-1-yl]-phenyl-methanone as an oil.

iii) [4-(2-Fluoro-ethyl)-piperidin-1-yl]-phenyl-methanone (17.1g) is dissolved in methanol (30ml), aqueous hydrochloric acid (6M, 60ml) is added and the mixture is heated at reflux for 72 hours. Methanol is removed by rotary evaporation and the remaining aqueous solution is washed with ethyl acetate (3x20ml). Solid sodium hydroxide is added to a final pH of 12 and the solution is extracted with ethyl acetate (3x25ml). The combined extracts are dried ($MgSO_4$) and evaporated to give 4-(2-fluoro-ethyl)-piperidine as a colourless oil after purification by vacuum distillation, b.p. 45°C/3mm.

b) 2(S)-Benzyloxycarbonylamino-3-benzothiazol-2-yl-propionic acid benzyl ester (10g) is dissolved in THF (60ml) and water (20ml), lithium hydroxide monohydrate (1.85g) and aqueous hydrogen peroxide (27.5%, 16ml) are added. The solution is kept at 20°C for 1 hour and sodium sulfite (17g) in water (50ml) is added slowly to the stirred mixture in an ice-bath. The solution is acidified to pH4 (conc. aqueous hydrochloric acid) and extracted with ethyl acetate (2x25ml). The combined organic extracts are washed with brine (50ml), dried ($MgSO_4$) and exaporated to dryness. The residue is triturated with ether (50ml) to afford 2(S)-benzyloxycarbonylamino-3-benzothiazol-2-yl-propionic acid as white crystals which are recrystallised from acetonitrile or tert.-butylmethylether.

c) 4-(2-Fluoro-ethyl)-piperidine hydrochloride (1.27g), 2(S)-benzyloxy-carbonylamino-3-benzothiazol-2-yl-propionic acid (2.70g) and PyBOP (3.93g) are dissolved in dry dichloromethane (100ml) and cooled in an ice-salt bath. Huenig Base (2.44g) is added and the reaction mixture is stirred

for 16 hours at 20°C. The solvent is removed by evaporation and the residue dissolved in ethyl acetate, washed with portions (50ml) of cold 10% aqueous citric acid, saturated aqueous sodium bicarbonate and brine. The organic phase is dried ($MgSO_4$), filtered and evaporated to dryness. Chromatography on a column of silicagel, using ethanol:ethyl acetate (1:9, by vol.) as eluant, gives pure 2(S)-benzyloxycarbonyl-amino-3-benzothiazol-2-yl-1-[4-(2-fluoro-ethyl)-piperidin-1-yl]-propan-1-one as a pale yellow oil.

d) A solution of 2(S)-benzyloxycarbonylamino-3-benzothiazol-2-yl-1-[4-(2-fluoro-ethyl)-piperidin-1-yl]-propan-1-one (1.64g) in glacial acetic acid (4.65ml) is stirred with hydrogen bromide in acetic acid (45% w/v, 9.3ml) for 2 hours at 20°C. tert.-Butylmethylether (75ml) is added and the mixture is stirred under nitrogen for 18 hours, the crystalline precipitate filtered off and washed with a little tert.-butylmethyl ether and triturated with diethyl ether to give pure 2(S)-amino-3-benzothiazol-2-yl-1-[4-(2-fluoro-ethyl)-piperidin-1-yl]-propan-1-one dihydrobromide. (Found C, 41.03; H, 5.13; N, 7.85; F, 3.75. $C_{17}H_{22}FN_3OS.2HBr$ requires C, 41.06, H, 4.86; N, 8.45; F, 3.82%).

e) 2(S)-Amino-3-benzothiazol-2-yl-1-[4-(2-fluoro-ethyl)-piperidin-1-yl]-propan-1-one dihydrobromide (16.4g) is dissolved in water (180ml) and ethyl acetate (90ml) is added. The pH is adjusted to 9 by addition of portions of aqueous sodium hydroxide (4M, ca. 21ml) with vigorous stirring. The organic layer is separated and the aqueous phase is extracted with ethyl acetate (2x100ml). The combined organic extracts are dried ($MgSO_4$) and evaporated to give 2(S)-amino-3-benzothiazol-2-yl-1-[4-(2-fluoro-ethyl)-piperidin-1-yl]-propan-1-one as a pale brown oil.

f) 2(S)-Amino-3-benzothiazol-2-yl-1-[4-(2-fluoro-ethyl)-piperidin-1-yl]-propan-1-one (13g) and NMM (11.1ml) are dissolved in dichloromethane (125ml) at 0-5°C and a solution of 4-chloro-pyridine-3-sulfonyl chloride (5.5g) is added

over a period of 30 minutes with cooling and addition of further NMM to maintain the mixture at pH9. The mixture is stirred at room temperature for 16 hours, filtered and the filtrate dried by rotary evaporation. The residue is dissolved in ethyl acetate (100ml), filtered to remove insoluble material, and the filtrate washed with aqueous acetic acid (10% v/v). The ethyl acetate is removed by rotary evaporation to give a solid which is recrystallised from aqueous ethanol to give 4-chloro-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide as a buff solid m.p. 152°C. $[M+H]^+$ = 511.0, 512.8.

g) 4-Chloro-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide (450mg) and 2(S)-amino-3-phenyl-propan-1-ol (532mg) are dissolved in ethanol (50ml) and the mixture is heated at reflux for 24 hours. After removal of solvent by rotary evaporation, the mixture is purified by flash chromatography on a column of silicagel using ethyl acetate:methanol (9:1, by vol.) as eluant to give 4-(1(S)-hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide as a white solid. $[M+H]^+$ = 626.3.

The following compounds are prepared similarly using appropriate starting materials. Spectral data acquired are consistent with claimed structures.

Example	Structure	$[M+H]^+$	NMR
1a	4-Butylamino-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	548.3	1H, 13C
1b	3-Propylamino-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-	533.9	1H, 13C

	piperidin-1-yl]-2-oxo-ethyl}-amide		
1c	5-Pentylamino-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	561.37	1H, 13C
1d	4-(3-Methyl-butylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	561.75	1H, 13C
1e	4-Isobutylamino-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	548.2	1H, 13C
1f	3-(3-{1(S)-Benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-propionic acid methyl ester	592	1H, 13C
1g	4-[2-(2-Hydroxy-ethoxy)-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	580.1	1H, 13C
1h	4-Benzylamino-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	582	1H, 13C
1i	4-Phenethylamino-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-	596.1	1H, 13C

	ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide		
1j	4-[2-(4-Methoxy-phenyl)-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	626.1	1H, 13C
1k	4-(4-Methyl-benzylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	595.44	1H, 13C
1l	4-(2-Amino-phenylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	582.6	1H, 13C
1m	4-(4-Phenyl-butylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	623.75	1H, 13C
1n	4-[2-(3,4-Dichloro-phenyl)-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	664.06; 666.06	1H, 13C
1o	4-[(3-{1(S)-Benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-methyl]-	640	1H, 13C

	benzoic acid methyl ester		
1p	4-(2-Amino-benzylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide		1H, 13C
1q	4-(2-Pyridin-2-yl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	596.37	1H, 13C
1r	4-[2-(4-Amino-phenyl)-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	610.8	1H, 13C
1s	4-[2-(4-Hydroxy-phenyl)-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	611.8	1H, 13C
1t	4-(1(S)-Hydroxymethyl-pentylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide		
1u	4-(1(R)-Hydroxymethyl-pentylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	591.8	

1v	12-(3-{1(S)-Benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-dodecanoic acid	690	1H, 13C
1w	4-(3,4-Dimethoxy-phenylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	628	1H, 13C
1x	4-[2-(2-Amino-phenyl)-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	610.1	1H, 13C
1y	4-[2-(3a,7a-Dihydro-1H-indol-3-yl)-1(S)-hydroxymethyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	665.4	
1z	4-[2-(3a,7a-Dihydro-1H-indol-3-yl)-1(R)-hydroxymethyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	665.3	
1aa	4-(1(S)-Hydroxymethyl-2-pyridin-3-yl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-	626.8	1H, 13C

	piperidin-1-yl]-2-oxo-ethyl}-amide		
1ab	4-[1(S)-Hydroxymethyl-2-(4-nitro-phenyl)-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	671.2	1H, 13C
1ac	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperazin-1-yl]-2-oxo-ethyl}-amide	627.9	
1ad	4-(2-Cyclohexyl-1(S)-hydroxymethyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	632.4	1H, 13C
1ae	4-(2-*trans*-Phenyl-cyclopropylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	608.6	1H, 13C
1af	4-(1(S)-Hydroxymethyl-3-methylsulfanyl-propylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	610.6	1H, 13C
1ag	4-(1(S)-Methoxymethyl-2-phenyl-ethylamino)-pyridine- 3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-	640.5	

	ethyl]-amide		
1ah	4-(5-Hydroxy-pentylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	579	1H, 13C
1ai	4-(4-Dimethylamino-phenylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	611.4	1H, 13C
1aj	4-(1(R)-Methyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	610.7	1H
1ak	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	624.4	
1al	4-(2-*trans*-Phenyl-cyclopropylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperazin-1-yl]-2-oxo-ethyl}-amide	609.6	1H, 13C
1am	4-(2-Hydroxy-phenylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	584.2	1H, 13C

1an	4-(2-Methylsulfanyl-phenylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	614.2	1H, 13C
1ao	4-{2-Phenyl-1(S)-[2-(tetrahydro-pyran-2(RS)-yloxy)-ethoxymethyl]-ethylamino}-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	755.2	
1ap	4-(2-*trans*-Phenyl-cyclopropylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	606	
1aq	4-(2-Cyclohexyl-1(S)-hydroxymethyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	630.6	
1ar	4-(1(R)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide		1H, 13C
1as	4-(1(S)-Hydroxymethyl-propylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	564.4	

1at	4-{2-Phenyl-1(S)-[2-(tetrahydro-pyran-2(RS)-yloxy)-ethoxymethyl]-ethylamino}-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	752.3	1H, 13C
1au	4-(1(R)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperazin-1-yl]-2-oxo-ethyl}-amide	627.4	
1av	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	642.1; 644.0	
1aw	4-(1(S)-Chloromethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	644.2; 646.2	1H, 13C
1ax	4-[1(S)-Hydroxymethyl-2-(4-hydroxy-phenyl)-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	642.3	1H, 13C
1ay	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-2-oxo-ethyl}-amide	625.3	1H, 13C

1az	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-naphthalen-2-ylmethyl-2-oxo-ethyl}-amide	619.4	1H, 13C
1ba	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-1(S)-pyridin-3-ylmethyl-ethyl}-amide	570.2	1H, 13C
1bb	4-[1(S)-Hydroxymethyl-2-(4-hydroxy-phenyl)-ethylamino]-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-naphthalen-2-ylmethyl-2-oxo-ethyl}-amide	635	
1bc	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	569.4	
1bd	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-1(S)-pyridin-2-ylmethyl-ethyl}-amide	570.4	1H, 13C
1be	3(S)-(3-{1(S)-Benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-4-phenyl-butyric acid .tert.-butyl ester	710.5	1H, 13C

1bf	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperazin-1-yl]-2-oxo-1(S)-pyridin-2-ylmethyl-ethyl}-amide	571.4	1H, 13C
1bg	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-1(S)-pyridin-4-ylmethyl-ethyl}-amide	570.3	1H, 13C
1bh	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	599.2	1H, 13C
1bi	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-cyclohexylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	575.5	1H, 13C
1bj	4-[1(S)-Hydroxymethyl-2-(4-methoxy-phenyl)-ethylamino]-pyridine-3-sulfonic acid {1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-2-phenyl-ethyl}-amide.	599.4	1H, 13C
1bk	4-[1(S)-Hydroxymethyl-2-(4-methoxy-phenyl)-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	656.3	1H, 13C
1bl	4-[1(S)-Hydroxymethyl-2-(4-methoxy-phenyl)-	600.4	1H, 13C

	ethylamino]-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-1(R)-pyridin-2-ylmethyl-ethyl}-amide		
1bm	4-[1(S)-(2-Hydroxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-2-phenyl-ethyl}-amide	613.5	1H, 13C
1bn	4-[1(S)-Hydroxymethyl-2-(4-methoxy-phenyl)-ethylamino]-pyridine-3-sulfonic acid [1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-2-(4-methoxy-phenyl)-ethyl]-amide	629.4	1H, 13C
1bo	4-[1(S)-Hydroxymethyl-2-(4-methoxy-phenyl)-ethylamino]-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-1(S)-pyridin-2-ylmethyl-ethyl}-amide	600.4	1H, 13C
1bp	4-[1(S)-(2-Hydroxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-2-pyridin-2-yl-ethyl}-amide	614.4	1H
1bq	4-[1(S)-(2-Hydroxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid [1(S)-[4-(2 fluoro-ethyl)-piperidine-1-carbonyl]-2-(4-methoxy-phenyl)-ethyl]-amide	643.4	1H
1br	4-(1(R)-Methyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-[4-(2-fluoro-ethyl)-	553.4	1H, 13C

	piperidine-1-carbonyl]-2-phenyl-ethyl}-amide		
1bs	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-ethoxy-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	612.9	1H
1bt	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-nitro-benzyl)-2-oxo-ethyl]-amide	614.4	1H, 13C
1bu	4-(2-Cyclohexyl-1(S)-hydroxymethyl-ethylamino)-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-1(S)-pyridin-2-ylmethyl-ethyl}-amide	576.4	1H, 13C
1bv	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-1(S)-pyridin-2-ylmethyl-ethyl}-amide	586.2	1H
1bw	4-(1(R)-Methyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-2-pyridin-2-yl-ethyl}-amide	554.5	1H, 13C
1bx	4-[2-(4-Ethoxy-phenyl)-1(S)-hydroxymethyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	613.3	1H, 13C

1by	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-1(S)-thiazol-4-ylmethyl-ethyl}-amide	576.2	1H, 13C
1bz	4-(2-Benzylsulfanyl-1(R)-hydroxymethyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	615.2	1H, 13C
1ca	4-(1(S)-Hydroxymethyl-3-phenyl-propylamino)-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-1(S)-pyridin-2-ylmethyl-ethyl}-amide	583.3	1H, 13C
1cb	4-[2-(4-Ethoxy-phenyl)-1(S)-hydroxymethyl-ethylamino]-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-1(R)-pyridin-2-ylmethyl-ethyl}-amide	614.4	1H, 13C
1cc	4-[2-(4-Ethoxy-phenyl)-1(S)-hydroxymethyl-ethylamino]-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-1(S)-pyridin-2-ylmethyl-ethyl}-amide	614.4	1H, 13C
1cd	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-fluoro-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	587.3	1H, 13C

1ce	4-(1(S)-Hydroxymethyl-3-phenyl-propylamino)-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-1(S)-pyridin-2-ylmethyl-ethyl}-amide	584.4	1H, 13C
1cf	4-(1(S)-Hydroxymethyl-3-phenyl-propylamino)-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-1(R)-pyridin-2-ylmethyl-ethyl}-amide	584.3	1H, 13C
1cg	4-(2-Benzylsulfanyl-1(R)-hydroxymethyl-ethylamino)-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-1(S)-pyridin-2-ylmethyl-ethyl}-amide	616.4	1H, 13C
1ch	4-(2-Benzylsulfanyl-1(R)-hydroxymethyl-ethylamino)-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-1(R)-pyridin-2-ylmethyl-ethyl}-amide	616.3	1H, 13C
1ci	4-[2-(4-Fluoro-phenyl)-1(S)-hydroxymethyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	587.2	1H, 13C
1cj	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzooxazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	610.2	1H, 13C
1ck	4-[2-(4-Fluoro-phenyl)-1(S)-hydroxymethyl-	588.2	1H, 13C

	ethylamino]-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-1(S)-pyridin-2-ylmethyl-ethyl}-amide		
1cl	4-[2-(4-Methoxy-phenyl)-1(R)-methyl-ethylamino]-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	613.3	1H, 13C
1cm	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-dimethylamino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	612.3	1H, 13C
1cn	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(3,4-dimethoxy-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	629.3	1H, 13C
1co	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzo[1,3]dioxol-5-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	613.2	1H, 13C
1cp	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-hydroxy-3-nitro-benzyl)-2-oxo-ethyl]-amide	630.2	1H, 13C
1cq	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-	585.1; 586.9	1H, 13C

	chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide		
1cr	4-[2-(3,4-Dimethoxy-phenyl)-1(S)-hydroxymethyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	629.3	1H
1cs	4-[1(S)-Hydroxymethyl-2-(4-methoxy-phenyl)-ethylamino]-pyridine-3-sulfonic acid {1(S)-(4-fluoro-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	617.3	1H, 13C
1ct	4-{1(S)-Benzyl-2-[4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazin-1-yl]-ethylamino}-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	764.5	1H, 13C
1cu	4-[2-(3,4-Dimethoxy-phenyl)-1(S)-hydroxymethyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-(4-fluoro-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	647.3	1H, 13C
1cv	4-[2-(3,4-Dimethoxy-phenyl)-1(S)-hydroxymethyl-ethylamino]-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	658.8	1H, 13C
1cw	4-[1(S)-(2-Hydroxy-ethoxymethyl)-2-phenyl-	631	1H, 13C

	ethylamino]-pyridine-3-sulfonic acid {1(S)-(4-fluoro-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide		
1cx	4-[1(S)-(2-Hydroxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid [2-[4-(2-chloro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	659.29	1H, 13C
1cy	4-[1(S)-(2-Hydroxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	625.4	1H, 13C
1cz	4-[1(S)-(2-Hydroxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	629.25	1H, 13C
1da	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-nitro-benzyl)-2-oxo-ethyl]-amide	614.3	1H, 13C
1db	4-(1(S)-Hydroxymethyl-3-methylsulfanyl-propylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	553.5	1H, 13C
1dc	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [1(S)-benzyl-2-(4-	551.4	1H, 13C

	ethyl-piperidin-1-yl)-2-oxo-ethyl]-amide		
1dd	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [1(S)-benzyl-2-(4-methyl-piperidin-1-yl)-2-oxo-ethyl]-amide	536.9	1H, 13C
1de	4-Ethylamino-pyridine-3-sulfonic acid [1(S)-benzyl-2-(4-ethyl-piperidin-1-yl)-2-oxo-ethyl]-amide	444.9	1H, 13C
1df	4-Amino-pyridine-3-sulfonic acid [1(S)-benzyl-2-(4-ethyl-piperidin-1-yl)-2-oxo-ethyl]-amide	417	1H, 13C
1dg	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [1(S)-benzyl-2-(3,4-dihydro-1.H.-isoquinolin-2-yl)-2-oxo-ethyl]-amide	570.7	1H, 13C
1dh	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [1(S)-benzyl-2-(6,7-dimethoxy-3,4-dihydro-1.H.-isoquinolin-2-yl)-2-oxo-ethyl]-amide	630.7	1H, 13C
1di	4-[1(S)-(2-Hydroxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	670.8	1H, 13C
1dj	4-[1(S)-(2-Hydroxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-	668.4	1H, 13C

	benzothiazol-2-ylmethyl-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide		
1dk	4-[(3-{1(S)-Benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-methyl]-benzoic acid	625.56	1H, 13C
1dl	4-Pentylamino-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	559.37	1H, 13C
1dm	4-Phenethylamino-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	593.75	1H, 13C
1dn	3(S)-(3-{1(S)-Benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-4-phenyl-butyric acid	654.4	1H, 13C
1do	3(S)-(3-{1(S)-Benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-4-phenyl-butyric acid	597.19	1H
1dp	4-(1(S)-Benzyl-3-hydroxy-propylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	640.3	

1dq	4-[2-(4-Amino-phenyl)-1(S)-hydroxymethyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	641.6	1H, 13C

Examples 1di and 1dj are obtained by acidic deprotection of Examples 1ao and 1at using standard conditions.

Examples 1dk and 1dn are obtained by alkaline deprotection of Examples 1o and 1be; 1dl and 1dm from the corresponding O-acetyl esters; and 1do from the corresponding methyl ester, using standard conditions.

Example 1dp is obtained by the action of borane:THF complex on Example 1dn.

Examples 1t and 1u, also 1y and 1z, are obtained by silicagel column chromatographic separation of diastereomeric mixtures resulting from reaction with racemic amines. In both cases, tentative stereochemical assignments are made on the bases of (i) the relative potencies of the pairs of compounds and (ii) their relative elution times on hplc analysis, by analogy with other diastereomeric pairs of known absolute configuration.

Examples 1bl and 1bo are tentatively assigned their stereochemistries by analogy of their potencies and chromatographic behaviours to diastereomeric pairs of known absolute configuration.

Example 1dq is obtained by catalytic reduction of Example 1ab

Examples 1cb and 1cc, 1ce and 1cf, and 1cg and 1ch are isolated by silicagel column chromatography of diastereomeric mixtures.

EXAMPLE 2

a) Analogously as described for Example 1(c) but using 3-(4-benzyloxy-phenyl)-2(S)-tert.-butoxycarbonylamino-propionic acid in place of 2(S)-benzyloxycarbonylamino-3-benzothiazol-2-yl-propionic acid and 4-(2-chloro-ethyl)-piperidine in place of 4-(2-fluoro-ethyl)-piperidine is prepared {2-(4-

benzyloxy-phenyl)-1(S)-[4-(2-chloro-ethyl)-piperidine-1-carbonyl]-ethyl}-carbamic acid tert.-butyl ester.

b) {2-(4-Benzyloxy-phenyl)-1(S)-[4-(2-chloro-ethyl)-piperidine-1-carbonyl]-ethyl}-carbamic acid tert.-butyl ester (1.84g) is dissolved in a solution of hydrogen chloride in ethanol (5.6M, 20ml) and the mixture is stirred at room temperature for 1 hour. Solvents are removed by rotary evaporation and toluene (25ml) is evaporated from the residue. The resulting foam is kept in vacuo over solid sodium hydroxide (pellets) for 2 hours to give 2(S)-amino-3-(4-benzyloxy-phenyl)-1-[4-(2-chloro-ethyl)-piperidin-1-yl]-propan-1-one hydrochloride.

c) Analogously as described for Example 1(f-g) but using 2(S)-amino-3-(4-benzyloxy-phenyl)-1-[4-(2-chloro-ethyl)-piperidin-1-yl]-propan-1-one hydrochloride in place of 2(S)-amino-3-benzothiazol-2-yl-1-[4-(2-fluoro-ethyl)-piperidin-1-yl]-propan-1-one dihydrobromide is prepared 4-(1(S)-hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-benzyloxy-benzyl)-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide.

d) 4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-benzyloxy-benzyl)-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide (0.184g) is dissolved in methanol (20ml) and hydrogenated (1 bar, 20°C, 24 hours) in the presence of 10% palladium on charcoal (100mg). After removal of catalyst by filtration and of the solvent by rotary evaporation, 4-(1(S)-hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-chloro-ethyl)-piperidin-1-yl]-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide is obtained as a white foam. $[M+H]^+$ = 601.3, 603.2.

The following compounds are prepared similarly:

Example	Structure	$[M+H]^+$	NMR
2a	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	585.3	1H, 13C
2b	4-[1(S)-(2-Hydroxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid [1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-2-(4-hydroxy-phenyl)-ethyl]-amide	629.3	1H
2c	4-[1(S)-Hydroxymethyl-2-(4-methoxy-phenyl)-ethylamino]-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	615.4	1H, 13C
2d	4-(2-Cyclohexyl-1(S)-hydroxymethyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	591.5	1H, 13C
2e	4-(1(R)-Methyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	569.3	1H, 13C
2f	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-hydroxy-benzyl)-2-	583.4	1H, 13C

	[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide		
2g	4-[2-(4-Methoxy-phenyl)-1(RS)-methyl-ethylamino]-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	599.3	1H, 13C
2h	4-[1(S)-(2-Hydroxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid [2-[4-(2-chloro-ethyl)-piperidin-1-yl]-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	645.2	1H
2i	4-[1(S)-(2-Hydroxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid [1(S)-[4-(2-hydroxy-ethyl)-piperidine-1-carbonyl]-2-(4-hydroxy-phenyl)-ethyl]-amide	627.4	1H
2j	4-[2-(4-Methoxy-phenyl)-1(R)-methyl-ethylamino]-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	599.3	1H, 13C
2k	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(3,4-dihydroxy-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	601.3	1H, 13C
2l	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	567.3	1H, 13C

2m	4-[2-(3,4-Dimethoxy-phenyl)-1(S)-hydroxymethyl-ethylamino]-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	645.5	1H, 13C
2n	4-[2-(3,4-Dimethoxy-phenyl)-1(S)-hydroxymethyl-ethylamino]-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	627.4	1H, 13C
2o	4-(1(S)-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	700.29	
2p	4-[1(S)-(2-Hydroxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	611.27	1H, 13C
2q	4-(2-trans-Phenyl-cyclopropylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	566.6	1H, 13C
2r	4-(1(S)-Hydroxymethyl-3-methylsulfanyl-propylamino)-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	550.7	1H, 13C

EXAMPLE 3

a) Analogously as described for Example 1(c) but using 2(S)-tert.-butoxycarbonylamino-3-pyridin-2-yl-propionic acid in place of 2(S)-benzyloxycarbonylamino-3-benzothiazol-2-yl-propionic acid is prepared {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-1(S)-pyridin-2-ylmethyl-ethyl}-carbamic acid tert.-butyl ester. This is treated as described for Example 2(b) to give 2(S)-amino-1-[4-(2-fluoro-ethyl)-piperidin-1-yl]-3-pyridin-2-yl-propan-1-one hydrochloride. This is treated as described for Example 1(f) to give 4-chloro-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-1(S)-pyridin-2-ylmethyl-ethyl}-amide.

b) 2(S)-Amino-3-(3,4-dimethoxy-phenyl)-propan-1-ol (57mg), Huenig Base (120µl) and 4-chloro-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-1(S)-pyridin-2-ylmethyl-ethyl}-amide (75mg) are dissolved in ethanol (5ml) and heated in a sealed vial at 90°C for 72 hours. The solvent is removed by rotary evaporation and the residue is purified by flash-chromatography on a column of silicagel using chloroform:methanol (19:1, by vol.) as eluant to give 4-[2-(3,4-dimethoxy-phenyl)-1(S)-hydroxymethyl-ethylamino]-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-1(S)-pyridin-2-ylmethyl-ethyl}-amide. $[M+H]^+$ = 630.3.

EXAMPLE 4

a) Analogously as described for Examples 1(c) and 2(b) but using 4-ethyl-piperidine and 2(S)-tert.-butoxycarbonylamino-3-(4-nitro-phenyl)-propionic acid in place of 4-(2-fluoro-ethyl)-piperidine hydrochloride and 2(S)-benzyloxy-carbonylamino-3-benzothiazol-2-yl-propionic acid is prepared 2(S)-amino-1-(4-ethyl-piperidin-1-yl)-3-(4-nitro-phenyl)-propan-1-one hydrochloride.

b) 2(S)-Amino-1-(4-ethyl-piperidin-1-yl)-3-(4-nitro-phenyl)-propan-1-one hydrochloride (9.2g) and Huenig Base (5.77ml) are dissolved in dichloromethane (80ml) and 4-chloro-pyridine-3-sulfonyl chloride (7.03g) is added to the solution which is stirred for 24 hours at room temperature. Water (100ml) and brine (100ml) are added, the organic phase is separated and the aqueous solution is extracted with dichloromethane (3x100ml). The combined extracts are dried ($MgSO_4$) and the solvent evaporated to give a brown waxy solid which is purified by flash chromatography on a column of silicagel using ethyl acetate:hexane (19:1, followed by 3:2, by vol.) as eluant to give 4-chloro-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-nitro-benzyl)-2-oxo-ethyl]-amide. $[M+H]^+$ = 480.9, 482.7.

c) (i) 2(S)-Dibenzylamino-3-phenyl-propan-1-ol (2g) and bromo-acetic acid tert.-butyl ester (3.77ml) are dissolved in dichloromethane (15ml) and to the stirred solution is added a solution of tetrabutylammonium hydrogen sulfate (2.05g) in aqueous sodium hydroxide (50% w/v, 25ml). The mixture is stirred at 20°C for 4 hours and water (150ml) is added. The mixture is extracted with ethyl acetate (200 then 4x100ml), the combined extracts are dried ($MgSO_4$) and the solvent evaporated to give a pale orange oil which is purified by flash chromatography on a column of silicagel using ether:hexane (19:1, followed by 10:1, by vol.) as eluant to give (2(S)-dibenzylamino-3-phenyl-propoxy)-acetic acid tert.-butyl ester as a colourless oil which is further purified by short path distillation (3mm Hg, 95°C). $[M+H]^+$ = 446.2.

(ii) (2(S)-Dibenzylamino-3-phenyl-propoxy)-acetic acid tert.-butyl ester (7.49g) is dissolved in dry THF (80ml) and lithium aluminium hydride in THF (1M, 67.2ml) is added to the stirred solution under an atmosphere of nitrogen keeping the temperature of the mixture below 5°C. The mixture

is allowed to warm to room temperature, excess of reagent is destroyed (water) and further water (200ml) is added. The mixture is extracted with ethyl acetate (350 + 100ml) and the combined extracts are washed with brine (200ml), dried ($MgSO_4$) and the solvent evaporated to give 2-(2(S)-dibenzylamino-3-phenyl-propoxy)-ethanol as a colourless oil. $[M+H]^+$ = 376.2.

(iii) 2-(2(S)-Dibenzylamino-3-phenyl-propoxy)-ethanol (6.22g) is dissolved in a mixture of methanol (75ml) and acetic acid (4ml) and the solution is hydrogenated (1 bar, 20°C, 17 hours) in the presence of 10% palladium on charcoal (1.18g). After removal of catalyst by filtration and of the solvent by rotary evaporation, 2-(2(S)-amino-3-phenyl-propoxy)-ethanol is obtained as a light orange oil. $[M+H]^+$ = 196.0.

d) 4-Chloro-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-nitro-benzyl)-2-oxo-ethyl]-amide (1g) is added to a stirred solution of 2-(2(S)-amino-3-phenyl-propoxy)-ethanol (934mg) and Huenig Base (3.62ml) in ethanol (5ml) and the reaction mixture is heated in a sealed vial at 100°C for 24 hours. Purification of crude recovered material by flash chromatography on a column of silicagel using dichloromethane:methanol (19:1, by vol.) as eluant provides 4-[1(S)-(2-hydroxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-nitro-benzyl)-2-oxo-ethyl]-amide as a pale yellow foam. $[M+H]^+$ = 640.6.

e) 4-[1(S)-(2-Hydroxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-nitro-benzyl)-2-oxo-ethyl]-amide (335mg) is dissolved in methanol (30ml) and the solution is hydrogenated (1 bar, 20°C, 17 hours) in the presence of 10% palladium on charcoal (80mg). After removal of catalyst by filtration and of the solvent by rotary evaporation, the crude product is purified by flash chromatography on a column of silicagel using dichloromethane:methanol (19:1, by vol.) as

eluant to give 4-[1(S)-(2-hydroxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid [1(S)-(4-amino-benzyl)-2-(4-ethyl-piperidin-1-yl)-2-oxo-ethyl]-amide as a white foam. $[M+H]^+$ = 610.4.

The following compounds are prepared similarly:

Example	Structure	$[M+H]^+$	NMR
4a	Methanesulfonic acid 2(S)-(3-{1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propyl ester	704.3	1H, 13C
4b	Toluene-4-sulfonic acid 2(S)-(3-{1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propyl ester	780.6	1H, 13C
4c	[2(S)-(3-{1(S)-Benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propoxy]-acetic acid tert.-butyl ester	683.4	1H
4d	4-(1(S)-Dimethylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	653.2	1H, 13C
4e	4-(1(S)-Morpholin-4-ylmethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	668.3	1H, 13C

4f	4-(1(S)-Benzyl-2-pyrrolidin-1-yl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	652.3	1H, 13C
4g	4-(1(S)-Morpholin-4-ylmethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-chloro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	684.3; 686.2	1H, 13C
4h	4-(1(S)-Morpholin-4-ylmethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	650.3	1H
4i	4-(1(S)-Morpholin-4-ylmethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-fluoro-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	656.1	1H
4j	4-(1(S)-Dimethylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	612.2; 614.2	1H
4k	4-(1(S)-Dimethylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	626.3	1H
4l	4-(1(S)-Dimethylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-chloro-	642.3; 644.2	1H

	ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide		
4m	4-(1(S)-Dimethylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	608.2	1H
4n	4-(1(S)-Dimethylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-fluoro-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	614.2	1H
4o	4-(2-Phenyl-1(S)-pyrrolidin-1-ylmethyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-chloro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	668.5; 670.5	1H, 13C
4p	4-(2-Phenyl-1(S)-pyrrolidin-1-ylmethyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-fluoro-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	640.6	1H, 13C
4q	4-(1(S)-Benzyl-2-pyrrolidin-1-yl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	622.2	1H, 13C
4r	4-[1(S)-Benzyl-2-(4-hydroxy-piperidin-1-yl)-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	668.2; 670.1	1H

4s	4-[1(S)-Benzyl-2-(4-hydroxy-piperidin-1-yl)-ethylamino]-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	682.1	1H
4t	4-[1(S)-Benzyl-2-(4-hydroxy-piperidin-1-yl)-ethylamino]-pyridine-3-sulfonic acid [2-[4-(2-chloro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	698.2; 700.2	1H
4u	4-[1(S)-Benzyl-2-(4-hydroxy-piperidin-1-yl)-ethylamino]-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	664.3	1H
4v	4-[1(S)-Benzyl-2-(4-hydroxy-piperidin-1-yl)-ethylamino]-pyridine-3-sulfonic acid {1(S)-(4-fluoro-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	670.1	1H
4w	4-{1(S)-Benzyl-2-[4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazin-1-yl]-ethylamino}-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	780.0; 782.0	1H, 13C
4x	4-{1(S)-Benzyl-2-[4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazin-1-yl]-ethylamino}-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	794.7	1H, 13C
4y	4-{1(S)-Benzyl-2-[4-(2-morpholin-4-yl-2-oxo-ethyl)-	810.7;	1H, 13C

	piperazin-1-yl]-ethylamino}-pyridine-3-sulfonic acid [2-[4-(2-chloro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	811.8	
4z	4-{1(S)-Benzyl-2-[4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazin-1-yl]-ethylamino}-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	776.4	1H, 13C
4aa	4-{1(S)-Benzyl-2-[4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazin-1-yl]-ethylamino}-pyridine-3-sulfonic acid {1(S)-(4-fluoro-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	782.1	1H, 13C
4ab	4-(1(S)-Benzyl-3-hydroxy-propylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	583	1H
4ac	4-(1(S)-Fluoromethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	628.6	
4ad	4-[1(S)-(2-Methoxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	627.23	1H
4ae	4-{1(S)-Benzyl-2-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-ethylamino}-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	711.36	1H, 13C

4af	4-{1(S)-Benzyl-2-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-ethylamino}-pyridine-3-sulfonic acid [2-[4-(2-chloro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	727.36; 728.44	1H, 13C
4ag	4-{1(S)-Benzyl-2-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-ethylamino}-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	697.4; 699.4	1H, 13C
4ah	4-(1(S)-Benzyl-4-hydroxy-butylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	596.9	1H
4ai	4-{1(S)-Benzyl-2-[4-(morpholine-4-carbonyl)-piperidin-1-yl]-ethylamino}-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	765.4; 767.4	
4aj	4-{1(S)-Benzyl-2-[4-(morpholine-4-carbonyl)-piperidin-1-yl]-ethylamino}-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	747.6	
4ak	4(S)-(3-{1(S)-Benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-5-phenyl-pentanoic acid	611.2	1H
4al	4(R)-(3-{1(S)-Benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-5-	611.2	

	phenyl-pentanoic acid		
4am	4-(1(S)-Morpholin-4-ylmethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	654.2	1H
4an	4-(1(S)-Morpholin-4-ylmethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	636.1	1H
4ao	4-(1(S)-Dimethylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	594.5	1H
4ap	4-[1(S)-Benzyl-2-(4-hydroxy-piperidin-1-yl)-ethylamino]-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	650.4	1H
4aq	4-{1(S)-Benzyl-2-[4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazin-1-yl]-ethylamino}-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	762	1H, 13C
4ar	4-{1(S)-Benzyl-2-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-ethylamino}-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	697.31	1H, 13C

4as	4-{1(S)-Benzyl-2-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-ethylamino}-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	679.41	1H, 13C
4at	4-(2-Phenyl-1(S)-pyrrolidin-1-ylmethyl-ethylamino)-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	620.4	1H, 13C
4au	4-(1(S)-Benzyl-2-pyrrolidin-1-yl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	638.3	1H, 13C
4av	[2(S)-(3-{1(S)-(4-Amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propoxy]-acetic acid	642.1	1H
4aw	4-[2-(4-Methoxy-phenyl)-1(S)-morpholin-4-ylmethyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	683.2	1H, 13C
4ax	4-(1(S)-Morpholin-4-ylmethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	669.1; 671.1	1H
4ay	4-(1(S)-Benzyl-3-hydroxy-propylamino)-pyridine-3-sulfonic acid [1(S)-(4-amino-benzyl)-2-(4-ethyl-piperidin-1-yl)-2-oxo-ethyl]-amide	580.1	1H

4az	4-[1(S)-(2-Methoxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid [1(S)-(4-amino-benzyl)-2-(4-ethyl-piperidin-1-yl)-2-oxo-ethyl]-amide	624.27	1H
4ba	4-(1(S)-Benzyl-4-hydroxy-butylamino)-pyridine-3-sulfonic acid [1(S)-(4-amino-benzyl)-2-(4-ethyl-piperidin-1-yl)-2-oxo-ethyl]-amide	593.7	1H
4bb	4-{1(S)-Benzyl-2-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-ethylamino}-pyridine-3-sulfonic acid [1(S)-(4-amino-benzyl)-2-(4-ethyl-piperidin-1-yl)-2-oxo-ethyl]-amide	677.9	1H, 13C
4bc	4-(1(S)-Benzyl-2-{4-[2-(2-hydroxy-ethoxy)-ethyl]-piperazin-1-yl}-ethylamino)-pyridine-3-sulfonic acid [1(S)-(4-amino-benzyl)-2-(4-ethyl-piperidin-1-yl)-2-oxo-ethyl]-amide	721.9	1H, 13C
4bd	4-(1(S)-Benzyl-2-pyrrolidin-1-yl-ethylamino)-pyridine-3-sulfonic acid [1(S)-(4-amino-benzyl)-2-(4-ethyl-piperidin-1-yl)-2-oxo-ethyl]-amide	619.4	1H, 13C
4be	4-(1(S)-Benzyl-2-pyrrolidin-1-yl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	653.3; 655.3	1H, 13C
4bf	(2(S)-{3-[1(S)-(4-Amino-benzyl)-2-(4-ethyl-piperidin-1-yl)-2-oxo-ethylsulfamoyl]-pyridin-4-ylamino}-3-phenyl-propoxy)-acetic acid	624.2	1H

4bg	4-(1(R)-Benzyl-4-hydroxy-butylamino)-pyridine-3-sulfonic acid [1(S)-(4-amino-benzyl)-2-(4-ethyl-piperidin-1-yl)-2-oxo-ethyl]-amide	593.8	1H
4bh	4-(1(S)-Morpholin-4-ylmethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-methyl-amide	652.6	1H
4bi	4-[1(S)-(2-Hydroxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-methyl-amide	626.8	1H
4bj	4-[1(S)-(2-Hydroxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methylamino-benzyl)-2-oxo-ethyl]-amide	642.33	1H, 13C
4bk	4-(1(S)-Methoxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methylamino-benzyl)-2-oxo-ethyl]-amide	611.7	1H, 13C
4bl	4-(1(S)-Dimethylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methylamino-benzyl)-2-oxo-ethyl]-amide	625.5	1H, 13C
4bm	4-[1(S)-(2-Hydroxy-ethoxymethyl)-2-phenyl-	623.9	1H, 13C

	ethylamino]-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-methylamino-benzyl)-2-oxo-ethyl]-amide		
4bn	4-{1(S)-Benzyl-2-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-ethylamino}-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-methylamino-benzyl)-2-oxo-ethyl]-amide	691.9	1H, 13C
4bo	4-(1(S)-Benzyl-2-{4-[2-(2-hydroxy-ethoxy)-ethyl]-piperazin-1-yl}-ethylamino)-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-methylamino-benzyl)-2-oxo-ethyl]-amide	735.9	13C
4bp	4-(1(S)-Benzyl-2-pyrrolidin-1-yl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methylamino-benzyl)-2-oxo-ethyl]-amide	651.3	1H, 13C
4bq	4-(1(S)-Diethylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methylamino-benzyl)-2-oxo-ethyl]-amide	653	1H, 13C
4br	[2(S)-(3-{1(S)-Benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propoxy]-acetic acid	627.5	1H
4bs	1-[2(S)-(3-{1(S)-Benzyl-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propyl]-piperidine-4-carboxylic	695.7; 697.7	1H, 13C

	acid		
4bt	1-(2(S)-{3-[2-[4-(2-Chloro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethylsulfamoyl]-pyridin-4-ylamino}-3-phenyl-propyl)-piperidine-4-carboxylic acid	725.6; 727.5	1H, 13C
4bu	1-[2(S)-(3-{1(S)-(4-Amino-benzyl)-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propyl]-piperidine-4-carboxylic acid	711.0: 713.2	1H, 13C
4bv	1-(2(S)-{3-[1(S)-(4-Amino-benzyl)-2-(4-ethyl-piperidin-1-yl)-2-oxo-ethylsulfamoyl] -pyridin-4-ylamino}-3-phenyl-propyl)-piperidine-4-carboxylic acid	675.2	1H, 13C
4bw	2-[2(S)-(3-{1(S)-Benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propoxy]-N-(2-hydroxy-ethyl)-acetamide	670.4	1H
4bx	4-[1(S)-(2-Morpholin-4-yl-2-oxo-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	696.3	1H
4by	2-[2(S)-(3-{1(S)-Benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propoxy]-N,N-dimethyl-acetamide	654.4	1H

4bz	4-[1(S)-(2-Morpholin-4-yl-2-oxo-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	711.5	1H
4ca	2-[2(S)-(3-{1(S)-(4-Amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propoxy]-N,N-dimethyl-acetamide	669.3	1H
4cb	[2(S)-(3-{1(S)-[4-(2-Fluoro-ethyl)-piperidine-1-carbonyl]-2-phenyl-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propoxy]-acetic acid	627.3	1H

Examples 4a to 4al omit the final hydrogenation step 4(e) of Example 4
Examples 4av and 4bf have a final saponification step
Example 4bd is a 77:23 mixture of diastereomers (by hplc analysis)
Example 4bg requires isolation by silicagel column chromatography from a mixture of diastereomers
Examples 4bh and 4bi - the assembly of both the N-methyl-amino acid and the
complex side chain are conducted before final assembly (See the analogous Example 7(e))
Examples 4bh to 4bq - the assembly of both the aminomethyl-substituted amino acid and the complex side chain are conducted before final assembly. Hydrogenolytic deprotection is the final step (See the analogous Example 7(e))
Examples 4br to 4bt require a final saponification step
Examples 4bu and 4bv require saponification to precede the final hydrogenation step

Examples 4bw to 4by - modification of the side chain of the amino pyridine substituent is effected by 1,1-carbonyl di-imadazole-assisted amide coupling as the last synthetic step

Examples 4bz and 4ca are as Examples 4bw to 4by with the addition of a final catalytic hydrogenation step

Example 4cb requires acidolytic deprotection as the final step

EXAMPLE 5

Analogously as described for Example 4(a-b) but using 4-(2-fluoro-ethyl)-piperidine in place of 4-ethyl-piperidine is prepared 4-chloro-pyridine-3-sulfonic acid {2-(4-[2-fluoro-ethyl]-piperidin-1-yl)-1(S)-(4-nitro-benzyl)-2-oxo-ethyl}-amide. This is treated with 2(S)-amino-3-phenyl-propan-1-ol analogously as described for Example 1 (g) and the product, 4-[1(S)-hydroxymethyl-2-phenyl-ethylamino]-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-nitro-benzyl)-2-oxo-ethyl}-amide is obtained as a pale yellow solid after purification by flash chromatography on a column of silicagel using dichloromethane:methanol (25:1, by vol.). This is reduced as described for Example 4(e) to give, after purification by flash chromatography on a column of silicagel using dichloromethane:methanol (25:1, by vol.) as eluant, 4-(1(S)-hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide. $[M+H]^+ = 584.4$.

The following compounds are prepared similarly:

Example	Structure	$[M+H]^+$	NMR
5a	4-(2-Cyclohexyl-1(S)-hydroxymethyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	590.3	1H, 13C
5b	4-[1(S)-Hydroxymethyl-2-(4-methoxy-phenyl)-ethylamino]-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	614.4	1H, 13C
5c	4-[1(S)-(2-Hydroxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	628.3	1H
5d	4-(1(R)-Methyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	568.3	1H, 13C
5e	4-[2-(4-Methoxy-phenyl)-1(R)-methyl-ethylamino]-pyridine-3-sulfonic acid {2-(4-amino-phenyl)-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-amide	598.3	1H, 13C
5f	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-(4-amino-phenyl)-	566.3	1H, 13C

	1(S)-(4-ethyl-piperidine-1-carbonyl)-ethyl]-amide		
5g	4-(2-Cyclohexyl-1(S)-hydroxymethyl-ethylamino)-pyridine-3-sulfonic acid [1(S)-(4-amino-benzyl)-2-(4-ethyl-piperidin-1-yl)-2-oxo-ethyl]-amide	572.2	
5h	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	600.1; 601.7	1H, 13C
5i	4-[1(S)-Hydroxymethyl-2-(4-methoxy-phenyl)-ethylamino]-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	630.0; 631.9	1H, 13C
5j	4-[1(S)-Hydroxymethyl-2-(4-methoxy-phenyl)-ethylamino]-pyridine-3-sulfonic acid [1(S)-(4-amino-benzyl)-2-(4-ethyl-piperidin-1-yl)-2-oxo-ethyl]-amide	596.7	1H, 13C
5k	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(3-amino-4-hydroxy-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	600.2	1H, 13C
5l	4-[1(S)-(2-Hydroxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid [1(R)-(4-amino-benzyl)-2-(4-ethyl-piperidin-1-yl)-2-oxo-ethyl]-amide	610.3	1H, 13C

5m	4-[2-(3,4-Dimethoxy-phenyl)-1(S)-hydroxymethyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	644.2	1H
5n	4-[2-(3,4-Dimethoxy-phenyl)-1(S)-hydroxymethyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	660.5; 662.5	1H
5o	4-[2-(3,4-Dimethoxy-phenyl)-1(S)-hydroxymethyl-ethylamino]-pyridine-3-sulfonic acid [1(S)-(4-amino-benzyl)-2-(4-ethyl-piperidin-1-yl)-2-oxo-ethyl]-amide	626.2	1H
5p	4-[1(S)-(2-Hydroxy-ethoxymethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	644.16	1H, 13C
5q	4-(2-*trans*-Phenyl-cyclopropylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	565.6	1H, 13C
5r	4-(1(S)-Methoxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	613.8	1H, 13C
5s	4-(1(S)-Hydroxymethyl-3-methylsulfanyl-	567.7	1H, 13C

	propylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide		
5t	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	582.2	1H

Example 5t is obtained by saponification of the 2-acetyloxyethyl precursor

The following are prepared by treatment of Example 5k with triethyl orthoformate and triethyl orthoacetate respectively under standard conditions.

5u	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzooxazol-5-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	610.3	1H
5v	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(2-methyl-benzooxazol-5-ylmethyl)-2-oxo-ethyl]-amide	624.4	1H, 13C

EXAMPLE 6

a) 4-[1(S)-Hydroxymethyl-2-phenyl-ethylamino]-pyridine-3-sulfonic acid {2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-nitro-benzyl)-2-oxo-ethyl}-amide (2.6g) is dissolved in dichloromethane (20ml), triethylamine (1.21ml) is added and the stirred mixture is cooled to 0°C under an atmosphere of nitrogen. Methanesulfonyl chloride (0.54ml) is added and the reaction is stirred at ice

temperature for 2 hours. The mixture is extracted with ethyl acetate (50ml), the extract is washed with aqueous hydrochloric acid (2M, 20ml) and saturated aqueous sodium bicarbonate (20ml), dried ($MgSO_4$) and solvent evaporated to give 4-(1(S)-methanesulfonylmethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-nitro-benzyl)-2-oxo-ethyl]-amide as a crisp, yellow foam. $[M+H]^+ = 647.2$.

b) 4-(1(S)-Methanesulfonylmethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-nitro-benzyl)-2-oxo-ethyl]-amide (450mg) is dissolved in ethanol (20ml), morpholine (4ml) is added and the mixture is heated at reflux for 4 hours. After removal of solvent by rotary evaporation, the residue is purified by flash chromatography on a column of silicagel using dichloromethane:methanol (19:1, by vol.) as eluant to give 4-(1(S)-morpholin-4-ylmethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-nitro-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide. $[M+H]^+ = 683.3$.

c) 4-(1(S)-Morpholin-4-ylmethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-nitro-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide is catalytically reduced as described for Example 4(e) to give 4-(1(S)-morpholin-4-ylmethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide. $[M+H]^+ = 653.1$.

The following compounds are prepared similarly:

Example	Structure	$[M+H]^+$	NMR
6a	4-(1(S)-Azidomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	651.3	1H, 13C

6b	4-(1(S)-Methylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	582.2	1H
6c	4-(1(S)-Dimethylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	596.2	1H
6d	4-[1(S)-Benzyl-2-(4-hydroxy-piperidin-1-yl)-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	652.4	1H
6e	4-(1(S)-Benzyl-2-pyrrolidin-1-yl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	638.2; 640.1	1H, 13C
6f	4-(2-Cyclohexyl-1(S)-methylaminomethyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	604.2; 606.1	1H, 13C
6g	4-{1(S)-Benzyl-2-[4-(morpholine-4-carbonyl)-piperidin-1-yl]-ethylamino}-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	749.3	1H, 13C
6h	Acetic acid 2-{1-[2(S)-(3-{1(S)-benzyl-2-[4-(2-	722.4	1H

	fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propyl]-piperidin-4-yl}-ethyl ester		
6i	4-(1(S)-Morpholin-4-ylmethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	638.2	1H, 13C
6j	4-(1(S)-Diethylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	624.3	
6k	4-(2-Cyclohexyl-1(S)-methylaminomethyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-chloro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	634.3; 636.3	1H, 13C
6l	1-[2(S)-(3-{1(S)-Benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propyl]-piperidine-4-carboxylic acid diethylamide	735.5	1H
6m	4-(1(S)-Diethylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	640.4; 642.4	1H, 13C
6n	4-[1(S)-Benzyl-2-(3-oxo-piperazin-1-yl)-ethylamino]-pyridine-3-sulfonic acid {1(S)-	651.3	1H, 13C

	benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide		
6o	4-(1(S)-Morpholin-4-ylmethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	654.2	1H, 13C
6p	4-[2-(4-Acetyl-piperazin-1-yl)-1(S)-benzyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	679.1	1H, 13C
6q	4-(1(S)-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	No parent ion	1H, 13C
6r	4-(2-Phenyl-1(S)-{[(pyridin-2-ylmethyl)-amino]-methyl}-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	659.6	1H, 13C
6s	4-(1(S)-Butylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-chloro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	670.5; 672.5	1H, 13C
6t	4-(1(S)-Butylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-	654.5	1H, 13C

	benzyl)-2-oxo-ethyl]-amide		
6u	4-{1(S)-Benzyl-2-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-ethylamino}-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	681.3	1H
6v	4-(1(S)-Diethylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	654.2	1H, 13C
6w	4-(1(S)-Benzyl-2-{4-[2-(2-hydroxy-ethoxy)-ethyl]-piperazin-1-yl}-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	725.4	1H
6x	4-(1(S)-Diethylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-chloro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	670.2; 672.2	1H, 13C
6y	4-(1(S)-Chloromethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	587.1; 589.6	1H
6z	4-(2-Phenyl-1(S)-{[(pyridin-4-ylmethyl)-amino]-methyl}-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	659.3	1H, 13C

6aa	1-[2(S)-(3-{1(S)-Benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propyl]-piperidine-4-carboxylic acid (2-methoxy-ethyl)-amide	737.3	1H, 13C
6ab	1-[2(S)-(3-{1(S)-Benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propyl]-piperidine-4-carboxylic acid propylamide	721.2	1H, 13C
6ac	4-(1(S)-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	714.2	1H
6ad	4-[2-(4-Acetyl-piperazin-1-yl)-1(S)-benzyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	696.1; 698.1	1H, 13C
6ae	4-[2-(4-Acetyl-piperazin-1-yl)-1(S)-benzyl-ethylamino]-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethyl]-amide	709.2	1H, 13C
6af	4-[2-(4-Acetyl-piperazin-1-yl)-1(S)-benzyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-(4-fluoro-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	697.31	1H, 13C
6ag	4-(1(S)-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-	700.2;	

	2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	702.2	
6ah	4-[1(S)-Benzyl-2-(3-oxo-piperazin-1-yl)-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	681.4; 683.4 $[M+CH_5]^+$	
6ai	4-[1(S)-(Methanesulfonylamino-methyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	No parent ion	1H, 13C
6aj	4-[1(S)-(2-Hydroxy-ethylsulfanylmethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	628.8	1H
6ak	4-[1(S)-Benzyl-2-(1,1-dioxo-thiomorpholin-4-yl)-ethylamino]-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	701.2	1H
6al	{[2(S)-(3-{1(S)-(4-Amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propyl]-methyl-amino}-acetic acid tert.-butyl ester	711.1	1H, 13C
6am	[(2(S)-{3-[2-[4-(2-Fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-hydroxyamino-benzyl)-2-oxo-	No parent	1H, 13C

	ethylsulfamoyl]-pyridin-4-ylamino}-3-phenyl-propyl)-methyl-amino]-acetic acid tert.-butyl ester	ion	
6an	{[2(S)-(3-{1(S)-(4-Amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propyl]-methyl-amino}-acetic acid	655.1	1H, 13C
6ao	1-(2(S)-{3-[2-[4-(2-Fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methoxy-benzyl)-2-oxo-ethylsulfamoyl]-pyridin-4-ylamino}-3-phenyl-propyl)-piperidine-4-carboxylic acid	709.8	
6ap	1-[2(S)-(3-{1(S)-(4-Fluoro-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propyl]-piperidine-4-carboxylic acid	697.8	
6aq	4-(1(S)-Dimethylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	612.4	1H, 13C
6ar	4-(2-Cyclohexyl-1(S)-methylaminomethyl-ethylamino)-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	586.3	1H, 13C
6as	4-(1(S)-Diethylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-(4-ethyl-	622.6	1H, 13C

	piperidin-1-yl)-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide		
6at	4-[2-(4-Acetyl-piperazin-1-yl)-1(S)-benzyl-ethylamino]-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	677.23	1H
6au	4-(1(S)-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide	682.4	1H, 13C
6av	4-(1(S)-Methylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	597.6	1H
6aw	4-(1(S)-Dimethylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	611.2	1H
6ax	4-(2-Phenyl-1(S)-propylaminomethyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	625.3	1H
6ay	4-(1(S)-Ethylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-	611.3	1H

	yl]-2-oxo-ethyl}-amide		
6az	4-(2-Cyclohexyl-1(S)-methylaminomethyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	603.3	1H, 13C
6ba	4-(1(S)-Butylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	639.4	1H
6bb	4-(1(S)-Benzyl-2-pyrrolidin-1-yl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	637.4	1H
6bc	4-(1(S)-Diethylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	639.4	1H
6bd	4-(2-Cyclohexyl-1(S)-dimethylaminomethyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	617.3	1H
6be	4-(2-Cyclohexyl-1(S)-ethylaminomethyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	617.4	1H

6bf	4-{1(S)-[(2-Hydroxy-ethylamino)-methyl]-2-phenyl-ethylamino}-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	627.3	1H
6bg	4-(2-Phenyl-1(S)-piperidin-1-ylmethyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	651.3	1H
6bh	4-(2-Phenyl-1(S)-thiomorpholin-4-ylmethyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	669.3	1H
6bi	4-(1(S)-Chloromethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	602.0; 604.0	1H
6bj	4-[1(S)-Benzyl-2-(4-hydroxy-piperidin-1-yl)-ethylamino]-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	667.2	1H
6bk	4-{1(S)-[(2-Methoxy-ethylamino)-methyl]-2-phenyl-ethylamino}-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	641.6	1H

6bl	4-(1(S)-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	699.6	1H
6bm	1-[2(S)-(3-{1(S)-(4-Amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propyl]-piperidine-4-carboxylic acid ethyl ester	723.2	1H
6bn	4-(1(S)-Morpholin-4-ylmethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [1(S)-(4-amino-benzyl)-2-(4-ethyl-piperidin-1-yl)-2-oxo-ethyl]-amide	635.3	1H, 13C
6bo	4-[2-(4-Acetyl-piperazin-1-yl)-1(S)-benzyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	694.2	1H
6bp	4-[2-(4-Acetyl-piperazin-1-yl)-1(S)-benzyl-ethylamino]-pyridine-3-sulfonic acid [1(S)-(4-amino-benzyl)-2-(4-ethyl-piperidin-1-yl)-2-oxo-ethyl]-amide	676.4	1H
6bq	4-(1(S)-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [1(S)-(4-amino-benzyl)-2-(4-ethyl-piperidin-1-yl)-2-oxo-ethyl]-amide	681.4	
6br	4-[1(S)-Benzyl-2-(3-oxo-piperazin-1-yl)-	648.6	

	ethylamino]-pyridine-3-sulfonic acid [1(S)-(4-amino-benzyl)-2-(4-ethyl-piperidin-1-yl)-2-oxo-ethyl]-amide		
6bs	4-[1(S)-Benzyl-2-(3-oxo-piperazin-1-yl)-ethylamino]-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	666.6	
6bt	4-[2-(4-Acetyl-piperazin-1-yl)-1(S)-benzyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-chloro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	710.4	
6bu	4-[1(S)-(2-Hydroxy-ethylsulfanylmethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	643.8	1H
6bv	1-[2(S)-(3-{1(S)-(4-Amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propyl]-piperidine-4-carboxylic acid	695	1H
6bw	.N.-(2(S)-{3-[2-[4-(2-Fluoro-ethyl)-piperidin-1-yl]-2-oxo-1(S)-(4-propionylamino-benzyl)-ethylsulfamoyl]-pyridin-4-ylamino}-3-phenyl-propyl)-N-methyl-propionamide	709.3	1H, 13C
6bx	4-{1(S)-[(3-Ethyl-ureido)-methyl]-2-phenyl-ethylamino}-pyridine-3-sulfonic acid {1(S)-	639.4	1H

	benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide		
6by	4-(2-Phenyl-1(S)-piperazin-1-ylmethyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	638.4	1H
6bz	4-[1(S)-(3-Ethyl-1-methyl-ureidomethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	668.4	1H
6ca	4-{1(S)-Benzyl-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-ethylamino}-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	680.3	1H
6cb	1-[2(S)-(3-{1(S)-Benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propyl]-piperidine-4-carboxylic acid	680.1 ($[M+Na]^+$)	1H, 13C
6cc	4-(1(S)-Mercaptomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	584.7	1H
6cd	4-(1(S)-Aminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	568.4	1H

6ce	4-(1(S)-Aminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzothiazol-2-ylmethyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	625.2	1H, 13C
6cf	4-[1(S)-(2-Hydroxy-ethylsulfanylmethyl)-2-phenyl-ethylamino]-pyridine-3-sulfonic acid [1(S)-(4-amino-benzyl)-2-(4-ethyl-piperidin-1-yl)-2-oxo-ethyl]-amide	626	1H
6cg	N-(2(S)-{3-[2-[4-(2-Fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-nitro-benzyl)-2-oxo-ethylsulfamoyl]-pyridin-4-ylamino}-3-phenyl-propyl)-N-methyl-acetamide	669.2	1H, 13C
6ch	N-[2(S)-(3-{1(S)-(4-Amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-ylamino)-3-phenyl-propyl]-N-methyl-acetamide	639.4	1H, 13C
6ci	4-(2-Cyclohexyl-1(S)-methylaminomethyl-ethylamino)-pyridine-3-sulfonic acid [1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-2-(4-fluoro-phenyl)-ethyl]-amide	606.3	1H, 13C
6cj	4-(1(S)-Diethylaminomethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-2-(4-fluoro-phenyl)-ethyl]-amide	641.9	1H

Examples 6a to 6ak, 6ci and 6cj omit the final hydrogenation step 6(e) of Example 6

Example 6al requires further elaboration of the aminopyridine substituent by alkylation with bromo-acetic acid tert.-butyl ester followed by reduction (as the last step of Example 5)

Example 6am is isolated as a by-product in the preparation of Example 6al

Example 6an is produced by acidolytic deprotection of Example 6al

Examples 6ao and 6ap require saponification as the last step

Examples 6aq to 6bu require catalytic hydrogenation as the last step (as Examples 2 or 5)

Example 6bb is a 60:40 mixture of diastereomers (by hplc analysis)

Example 6bc is an 80:20 mixture of diastereomers (by hplc analysis)

Example 6bv is prepared as Examples 6aq to 6bu followed by a saponification step

Example 6bw is obtained by the treatment of Example 6av with propionyl chloride

Examples 6bx is obtained by treatment of Example 6cd with ethyl isocyanate

Example 6by requires acidolytic deprotection of the tert.-butoxycarbonyl precursor

Example 6bz is obtained after treament of the appropriate precursor with ethyl isocyanate followed by catalytic hydrogenation (as the last step of Example 5)

Examples 6ca and 6cb are obtained by a final saponification step

Examples 6cd to 6cf require a final hydrogenation step

Example cg is obtained by acetylation of the appropriate precursor

Example ch is obtained by catalytic reduction of Example 6cg

EXAMPLE 7

a) Analogously as described for Example 1(c) but using 3-(4-nitro-phenyl)-2(S)-tert.-butoxycarbonylamino-propionic acid in place of 2(S)-benzyloxycarbonylamino-3-benzothiazol-2-yl-propionic acid is prepared {2-(4-

nitro-phenyl)-1(S)-[4-(2-fluoro-ethyl)-piperidine-1-carbonyl]-ethyl}-carbamic acid tert.-butyl ester. This is catalytically reduced as described for Example 4(e) to give {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-carbamic acid tert.-butyl ester.

b) A mixture of {1(S)-(4-amino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-carbamic acid tert.-butyl ester (2g), titanium tetra-isopropoxide (2ml) and benzaldehyde (0.85ml) is stirred at room temperature for 2 hours and ethanol (20ml) is added. Sodium cyanoborohydride (1g) is added and the mixture is stirred at room temperature for 16 hours. Water (20ml) is added and solids removed by filtration. The filtrate is diluted with ethyl acetate (100ml), the organic layer is separated, washed with water (50ml), dried ($MgSO_4$) and the solvent evaporated to give a residue which is purified by flash chromatography on a column of silicagel using hexane:ethyl acetate (1:1, by vol.) as eluant to give {1(S)-(4-benzylamino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-carbamic acid tert.-butyl ester as a yellow foam.

c) {1(S)-(4-Benzylamino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-carbamic acid tert.-butyl ester (1.51g) is dissolved in acetonitrile (20ml) and aqueous fomaldehyde (37% w/v, 1.5ml) and sodium cyanoborohydride (615mg) are added followed by glacial acetic acid (1ml). The mixture is stirred at room temperature for 1 hour, further portions of aqueous fomaldehyde (37% w/v, 1.5ml) and sodium cyanoborohydride (615mg) are added and the mixture is stirred for a further 30 minutes. The mixture is extracted with ether (50ml). The extract is washed with aqueous sodium hydroxide (M, 25ml), dried ($MgSO_4$) and evaporated to give (3-{1(S)-[4-(benzyl-methyl-amino)-benzyl]-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethylsulfamoyl}-pyridin-4-yl)-carbamic acid tert.-butyl ester as a yellow oil which is deprotected as described for Example 2(b) to give 2(S)-amino-3-[4-

(benzyl-methyl-amino)-phenyl]-1-[4-(2-fluoro-ethyl)-piperidin-1-yl]-propan-1-one hydrochloride as a white foam.

d) Analogously as described for Example 1(f-g), 2(S)-amino-3-[4-(benzyl-methyl-amino)-phenyl]-1-[4-(2-fluoro-ethyl)-piperidin-1-yl]-propan-1-one hydrochloride is converted to 4-(1(S)-hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-[4-(benzyl-methyl-amino)-benzyl]-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide. The product is isolated by flash chromatography on a column of silicagel using dichloromethane:methanol (25:1, by vol.) as eluant.

e) 4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-[4-(benzyl-methyl-amino)-benzyl]-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide (750mg) is dissolved in ethanol (25ml) and the mixture is hydrogenated (1 bar, 20°C, 120 hours) in the presence of 10% palladium on charcoal (100mg). After removal of catalyst by filtration and of solvent by rotary evaporation, the residue is purified by flash chromatography on a column of silicagel using dichloromethane:methanol (20:1, by vol.) as eluant to give 4-(1(S)-hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methylamino-benzyl)-2-oxo-ethyl]-amide as a white solid. $[M+H]^+$ = 598.3.

The following compounds are prepared similarly, by pre-assembly of the amino acid component (steps a-c) before final assembly, analogous to steps d and e (where appropriate):

Example	Structure	$[M+H]^+$	NMR
7a	N-(4-{3-[4-(2-Fluoro-ethyl)-piperidin-1-yl]-2(S)-[4-(1(S)-hydroxymethyl-2-phenyl-ethylamino)-	626.3	1H, 13C

	pyridine-3-sulfonylamino]-3-oxo-propyl}-phenyl)-acetamide		
7b	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-(4-ethylamino-benzyl)-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-amide	612.2	1H, 13C
7c	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-formylamino-benzyl)-2-oxo-ethyl]-amide	612.1	1H, 13C
7d	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid {1(S)-benzyl-2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-methyl-amide	582.8	1H
7e	4-(1(S)-Hydroxymethyl-2-phenyl-ethylamino)-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-methylamino-benzyl)-2-oxo-ethyl]-amide	579.8	1H, 13C
7f	4-[1(S)-Hydroxymethyl-2-(4-methoxy-phenyl)-ethylamino]-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-methylamino-benzyl)-2-oxo-ethyl]-amide	609.7	1H, 13C
7g	4-[2-(3,4-Dimethoxy-phenyl)-1(S)-hydroxymethyl-ethylamino]-pyridine-3-sulfonic acid [2-(4-ethyl-piperidin-1-yl)-1(S)-(4-	640	1H, 13C

	methylamino-benzyl)-2-oxo-ethyl]-amide		
7h	4-[2-(3,4-Dimethoxy-phenyl)-1-(S)hydroxymethyl-ethylamino]-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methylamino-benzyl)-2-oxo-ethyl]-amide	658.5	1H, 13C
7i	4-[1(S)-Hydroxymethyl-2-(4-methoxy-phenyl)-ethylamino]-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methylamino-benzyl)-2-oxo-ethyl]-amide	628.2	1H, 13C
7j	4-(2-Cyclohexyl-1(S)-hydroxymethyl-ethylamino)-pyridine-3-sulfonic acid [2-[4-(2-fluoro-ethyl)-piperidin-1-yl]-1(S)-(4-methylamino-benzyl)-2-oxo-ethyl]-amide	604.4	1H, 13C

EXAMPLE 8

Determination of the potency of the compounds.

K_i value:

The compounds are analysed for their effect on the human α-thrombin-catalysed hydrolysis of the substrate Kabi S-2238 (Kabi Vitrum (UK) Ltd). The K_m and K_p values are derived from a Lineweaver-Burk plot of data, from which is calculated the K_i value for the inhibitors. The potency of compounds with respect to human α-thrombin is expressed as their kinetic inhibition constant (K_i).

Duplicate series of reaction mixtures are prepared comprising chromogenic substrate S-2238 (Kabi Vitrum) in Tris/HCl buffer (0.05M, pH 8.4) with a range of concentrations of substrate from 3.125μM to 100μM. The solutions are brought to 37°C in a thermostatically regulated heating block. Into one of the sets of duplicates is added inhibitor dissolved in a compatible vehicle (water, methanol or DMSO) to give a final concentration close to the expected K_i, and into the second series is added an equivalent volume of the vehicle alone. The reactions are started by the addition of human α-thrombin (Sigma, T-8885) to give a final activity of 0.0625 NIH units/ml. Following mixing by inversion, the initial reaction rate (as change in absorbance per minute) is measured using a Perkin Elmer Lambda 5 spectrophotometer (fitted with a cuvette holder thermostatted at 37°C) at 405nm over a period of 1 minute during which time the rate is linear and showing no signs of substrate depletion.

APTT value:

Freshly collected blood is immediately anticoagulated by mixing with one-tenth volume of trisodium citrate solution (3.8% w/v in distilled water). The blood is centrifuged at 1300 x g for 20 minutes to obtain platelet-poor plasma.

Aliquots of plasma are treated with solutions of experimental compound or vehicle alone to give a range of concentrations from 0 to approximately 150μM. The APTTs of the treated plasma samples are determined using the standard method on the Instrumentation Laboratory ACL 300R coagulometer. The principle of the assay is that citrated plasma (50μl) is activated by incubating for 5 minutes at 37°C with bovine cephalin reagent (Instrumentation Laboratory (UK) Ltd, APTT (Ellagic Acid) Test Kit, 50μl), before initiating coagulation by the addition of calcium chloride solution (20mM, 50μl). The time taken for coagulation of the plasma to occur is measured automatically by the Instrumentation Laboratory ACL 300R

coagulometer. The concentration of each compound required to double the APTT of the plasma is determined from a graph of concentration of experimental compound *vs* APTT.

Table Potency (K_i and APTT) against human thrombin

Ex	K_i (nM)	APTT (μM)
1	6	4.3
1aa	14	3.5
1ac	48	4.6
1bk	7	3.7
1bo	58	2.8
1bp	175	4.8
1bv	39	4.4
1ct	112	4.6
1di	8	3.2
2	36	4.5
2a	41	1.7
2b	82	4.0
2c	30	4.3
2d	16	3.8
2h	28	4.4
2m	7	3.4
3	30	4.6
4	96	5.0
4aa	70	4.6
4ae	28	4.5
4ar	58	2.3
4au	32	3.7
4av	197	3.8
4aw	16	1.8
4ax	12	2.6
4ba	115	1.8
4bb	-	5.0

Ex	K_i (nM)	APTT (μM)
4bj	23	4.6
4bl	20	4.3
4bp	14	3.2
4bq	-	4.0
4bs	33	2.2
4bt	9	2.5
4bu	-	1.2
4bv	-	1.5
4bz	46	2.0
4ca	47	2.3
4e	55	4.3
4f	16	3.8
4s	8	3.3
4v	40	4.0
5	13	2.5
5a	18	2.7
5b	20	2.9
5c	49	2.5
5h	27	4.5
5i	16	3.3
5j	40	5.0
5k	26	1.5
5m	13	3.8
5n	9	4.2
5p	52	2.5
5r	31	4.3
6	29	2.6

Ex	K_i (nM)	APTT (μM)
6ak	-	2.1
6ao	6	1.5
6ap	75	1.6
6at	60	4.5
6av	35	2.5
6aw	25	3.5
6ax	47	3.3
6ay	99	3.2
6az	33	2.8
6bb	487	3.4
6bc	45	3.6
6bd	40	4.2
6be	83	4.8
6bf	72	2.0
6bj	19	1.7
6bo	24	2.4
6bp	63	2.9
6br	225	3.3
6bs	99	2.4
6bt	-	2.0
6bu	-	2.2
6bv	24	1.9
6cb	52	1.8
6ce	10	3.5
6ch	110	3.4
6d	61	4.9
7	12	4.1

EXAMPLE 9

Using active substances as described in any of the foregoing Examples, the following dosage forms are made.

Tablets suitable for oral administration.

Tablets containing the ingredients indicated below may be prepared by conventional techniques.

Ingredient	Amount per Tablet (mg)
Active substance	250
Lactose	140
Corn starch	35
Talcum	20
Magnesium stearate	5
Total	450 mg

EXAMPLE 10

Capsules for oral administration

Capsules of the below are made up by thoroughly mixing together batches of the ingredients and filling hard gelatin capsules with the mixture

Ingredient	Amount per Capsule (mg)
Active substance	250
Lactose	250
Total	500 mg

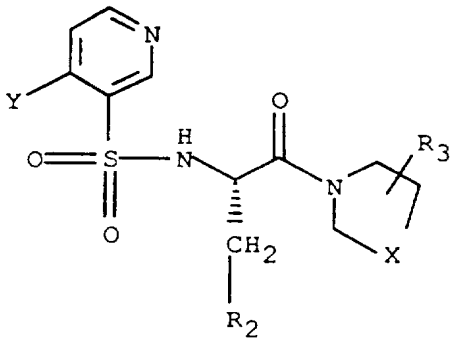
EXAMPLE 11

The following ingredients are dissolved in water for intravenous perfusion and the resulting solution is then sterilized

Ingredient	(mg)
Active substance	0.25
Buffer system	as desired
Glucose	25
Distilled water	500

Claims

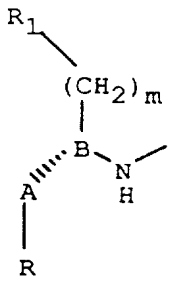
1. A compound of the general formula I



(I)

in which Y is a primary or secondary amino group; R_2 is the residue of a natural or synthetic amino acid; R_3 is hydrogen or a C_1-C_8 alkyl chain which may be substituted by hydroxy or halogen; and X is $(CH_2)_n$ where n is 1, 2, or 3, or is CH_2N or represents a fused phenyl ring which is optionally substituted by one or two methoxy groups or a salt thereof.

2. A compound as claimed in claim 1 in which Y has the formula



(II)

in which A and R are absent or A is a methylene or ethylene group, and R is hydrogen, halogen, azido, $COOR_8$ where R_8 is H or alkyl, OR_9 where R_9 is H, alkyl, optionally substituted hydroxyalkyl, optionally substituted carboxyalkyl, optionally substituted amidoalkyl, SO_2 alkyl, SO_2 aryl, or $NR_{10}R_{11}$ where R_{10} and R_{11} are independently H, alkyl which is optionally substituted and/or optionally interrupted by O or is CH_3SO_2, or together with the nitrogen atom form an optionally substituted ring which may contain another hetero atom

or R is SR_{12} where R_{12} is hydrogen or hydroxyalkyl; B is CH or is absent provided that when B is absent, A and R are also absent; R_1 is hydrogen, alkyl, alkyl optionally substituted and/or optionally interrupted by O, S, carboxyl aminocarbonyl, or carbonylamino or is an optionally substituted phenyl ring or a phenyl ring containing one or more heteroatoms or a cyclohexane or bicyclic ring containing one or more hetero atoms; m is 0, 1 or 2 and when m is 1 and R is H, A may form a cyclopropane ring with the C atom to which R_1 is attached.

3. A compound as claimed in claim 2 in which R_{10} and R_{11} represent alkyl, alkyl optionally substituted by OH, $COOR_8$ where R_8 is H or alkyl, carbonyl or amide groups or by a heterocyclic ring.

4. A compound as claimed in claim 2 or 3 in which R_1 is an alkyl group substituted by OH, substituted hydroxyl, carboxyl, carboxyalkyl, phenyl or substituted amino.

5. A compound as claimed in claim 2 or 3 in which R_1 is a phenyl ring substituted by one or more halogen or alkyl groups or one or more groups OR_4. SR_5, NR_6R_7 or $COOR_8$ where each of R_4 to R_8 is H or alkyl or NR_6R_7 is NO_2.

6. A compound as claimed in any one of claims 2 to 5 in which R is selected from H, F, Cl, N_3, OH, OCH_3, OSO_2CH_3, OCH_2CH_2OH and its 2-pyranyl ether, OCH_2COOH and its tert.-butyl ester, $OCH_2CON(CH_3)_2$, $OCH_2CONH(CH_2)_2OH$, the corresponding morpholide $OCH_2COMorph$, COOH and its methyl and tert.-butyl esters, SH, $S(CH_2)_2$ OH, $S(CH_2)_3$ OH, NH_2, $NHCH_3$, NHC_2H_5, $N(CH_3)C_2H_5$, $NHC_3H_7(n)$, NHC_4H_9, $NHCH_2CH_2OH$, $NHCONH_2$, $NHCONHC_2H_5$, $NHCH_2CH_2OCH_3$, $N(CH_2CH_2OCH_3)_2$, $NHCOCH_3$, $N(CH_3)CH_2COOH$, $NHCH_2COOH$ and its tert.-butyl ester, $NHCH_2$ pyridyl, $N(CH_3)_2$, $N(C_2H_5)_2$, pyrrolidinyl, piperidinyl, 4-hydroxypiperidinyl, morpholinyl and thiomorpholinyl.

7. A compound as claimed in any preceding claim in which R_1 is derived from optionally ring-substituted phenylalanines, tryptophans and pyridylalanines.

8. A compound as claimed in any one of claims 2 to 7 in which the group R_1-$(CH_2)_m$ is n-propyl, n-butyl, n-pentyl, iso-butyl, iso-pentyl, 5-hydroxy-pentyl, carboxylethyl, 4-phenylbutyl, n-butylcarbamoylethyl, 2-indanyl, 4-methylbenzyl, 2-aminobenzyl, 4-carboxybenzyl and its methyl ester, 2-pyridylmethyl, phenylethyl, 4-hydroxyphenylethyl and its methyl ether, 2-aminophenylethyl, carboxyundecyl or hydroxyethyloxyethyl.

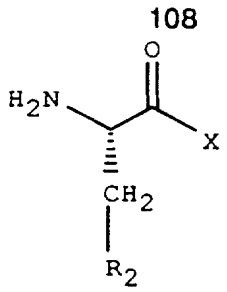
9. A compound as claimed in any preceding claim in which R_2 is derived from the amino acids phenylalanine, tyrosine, dopa and its ethers such as the methylenedioxy ether, p-aminophenylalanine, p-nitrophenylalanine, naphthylalanine, benzothiazolylalanine, thiazolylalanine, cyclohexylalanine, the pyridylalanines, tryptophan, and fused 6/5 membered ring systems linked through the 6-membered ring and where the 5-membered ring contains one or more hetero atoms.

10. A compound as claimed in any preceding claim in which the group R_3 has 2 or 3 carbon atoms and is optionally terminally substituted by hydroxy, fluorine or chlorine.

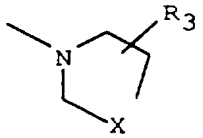
11. A compound as claimed in any one of claims, 2 to 10 in which A-R is present, m is 1, A is -CH_2- and X is $(CH_2)_2$.

12. A compound as claimed in any preceding claim which has the (S) configuration at each of the chiral centres.

13. A process for producing a compound of formula I as defined in claim 1 which comprises reacting 4-chloropyridine-3-sulfonyl chloride with an aminoacid of formula



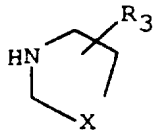
where X is -OH, protected OH or



and then reacting the resulting product with an amine of the formula

YH

and finally, if necessary, reacting with a base of the formula



14. A pharmaceutical composition comprising a compound of formula I as defined in claim 1 together with a pharmaceutically acceptable carrier or diluent.

15. A compound of formula I as defined in claim 1 substantially as hereinbefore described with reference to any one of the foregoing Examples.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 97/01385

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/12 C07D213/73 A61K31/44 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 555 824 A (DR. KARL THOMAE) 18 August 1993 see example 23	1-15
A	FR 2 727 413 A (SYNTHELABO) 31 May 1996	
A	WO 94 12181 A (MERCK) 9 June 1994	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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INTERNATIONAL SEARCH REPORT

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